### Subpart C—Injectable Dosage Forms

**Subparts D–J—[Reserved]**

**Subpart K—Bulk Drug Formulations for Repacking or for Manufacturing Use**



AUTHORITY: Sec. 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357).

## Subpart A—Bulk Drugs

### § 440.1a Sterile azlocillin sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile azlocillin sodium is the sodium salt of 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[[[[(2-oxo-1-imidazolidinyl)carbonyl] amino]phenylac-etyl]amino]-[2*S*-[2α,5α,6β(*S**)]]-. It is so purified and dried that:

(i) If the azlocillin sodium is not packaged for dispensing, its azlocillin content is not less than 859 micrograms and not more than 1,000 micrograms of azlocillin per milligram on an anhydrous basis. If the azlocillin sodium is packaged for dispensing, its azlocillin content is not less than 859 micrograms and not more than 1,000 micrograms of azlocillin per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 115 percent of the number of milligrams of azlocillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 2.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams of azlocillin per milliliter is not less than 6.0 and not more than 8.0.

(vi) Its specific rotation in an aqueous solution containing 10 milligrams of azlocillin per milliliter is +170° to +200°.

(vii) It gives a positive identity test for azlocillin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, specific rotation, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except:

(i) *Dilute Brij 35 solution.* In lieu of the hydroxylamine hydrochloride solution described in § 442.40(b)(1)(ii)(*b*)(*1*) of this chapter, use dilute Brij 35 solution in the reference channel. Prepare dilute Brij 35 solution as follows: Place 1 milliliter of Brij 35, 30 percent solution, into a 1-liter volumetric flask containing 900 milliliters of distilled water. Swirl gently and dilute to volume slowly with distilled water. Mix well.

(ii) *Buffer.* In lieu of the buffer described in § 442.40(b)(1)(ii)(*b*)(*2*) of this chapter, use the buffer prepared as follows: Dissolve 200 grams of primary standard tris (hydroxymethyl) aminomethane in sufficient distilled water to make 1 liter. Filter before use.

(iii) *Preparation of working standard solution.* Dissolve and dilute an accurately weighed portion of the azlocillin working standard with sufficient distilled water to obtain a concentration

of 1.0 milligram of azlocillin per milliliter.

(iv) *Preparation of sample solutions*—(*a*) *Product not packaged for dispensing (micrograms of azlocillin per milligram).* Dissolve and dilute an accurately weighed portion of the sample with sufficient distilled water to obtain a stock solution of 1.0 milligram of azlocillin per milliliter (estimated).

(*b*) *Product packaged for dispensing.* Determine both micrograms of azlocillin per milligram of the sample and milligrams of azlocillin per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(iv)(*b*)(*1*) and (*2*) of this section.

(*1*) *Micrograms of azlocillin per milligram.* Dissolve and dilute an accurately weighed portion of the sample with sufficient distilled water to obtain a stock solution of 1.0 milligram of azlocillin per milliliter (estimated).

(*2*) *Milligrams of azlocillin per container.* Reconstitute as directed in the labeling using distilled water in lieu of the reconstituting fluid. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to a concentration of 1.0 milligram of azlocillin per milliliter (estimated).

(v) *Calculations*—(*a*) Calculate the micrograms of azlocillin per milligram of sample as follows:

$$\text{Micrograms of azlocillin per milligram of sample} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100_{-m})}$$

where:

$A_u$=Absorbance of sample solution;
$P_s$=Potency of working standard solution in micrograms per milliliter;
$A_s$=Absorbance of working standard solution;
$C_u$=Milligrams of sample per milliliter of sample solution; and
$m$=Percent moisture in sample.

(*b*) Calculate the azlocillin content of the single-dose vial as follows:

$$\text{Milligrams of azlocillin per vial} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Absorbance of sample solution;
$P_s$=Potency of working standard solution in micrograms per milliliter;
$A_s$=Absorbance of working standard solution; and
$d$=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(b) of this chapter, using a solution containing 100 milligrams of azlocillin per milliliter.

(4) *Moisture.* Proceed as directed in §436.201 of this chapter, using the titration procedure and calculations described in paragraph (e)(2) of that section and preparing the sample as follows: Weigh the vial. Rapidly transfer a portion of the powder into the titration vessel, add the Karl Fischer reagent and restopper the vial immediately. Reweigh the vial to obtain the sample weight. A nitrogen purged glove bag or glove box should be used for preparing the sample.

(5) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams of azlocillin per milliliter.

(6) *Specific rotation.* Proceed as directed in §436.210 of this chapter, using an aqueous solution containing 10 milligrams of azlocillin per milliliter and a 1.0-decimeter polarimeter tube. Calculate the specific rotation on an anhydrous basis.

(7) *Identity.* Proceed as directed in §436.336 of this chapter.

[47 FR 53348, Nov. 26, 1982, as amended at 50 FR 1504, Jan. 11, 1985; 55 FR 11582, Mar. 29, 1990]

### §440.2a Sterile amdinocillin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile amdinocillin is 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1*H*-azepin-1-yl)-methylene]amino]-3,3-dimethyl-7-

oxo-, [2*S*-2α,5α,6β)]-. It is so purified and dried that:

(i) If the amdinocillin is not packaged for dispensing, its amdinocillin potency is not less than 950 micrograms and not more than 1,050 micrograms of amdinocillin per milligram on an anhydrous basis. If the amdinocillin is packaged for dispensing, its amdinocillin potency is not less than 950 micrograms and not more than 1,050 micrograms of amdinocillin per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of amdinocillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 0.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams of amdinocillin per milliliter is not less than 4.0 and not more than 6.2.

(vi) It is crystalline.

(vii) It gives a positive identity test for amdinocillin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for amdinocillin potency, and if packaged for dispensing, amdinocillin potency and container content, sterility, pyrogens, moisture, pH, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 25 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Amdinocillin potency and container content.* Proceed as directed in § 436.353 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 220 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, e.g., a Whatman ODS–3 column (25-centimeter column having an inside diameter of 4.6 millimeters and 5 micrometer particle size or equivalent), a flow rate of 1.0 milliliter per minute, and an injection volume of 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(*a*) *Buffer solution 0.01M pH 5.0.* Transfer 1.36 grams of monobasic potassium phosphate in sufficient water to make 1,000 milliliters of solution. Adjust the pH to 5.0 ± 0.1 with 18*N* phosphoric acid or 10*N* sodium hydroxide.

(*b*) *Mobile phase.* Mix acetonitrile (high-pressure liquid chromatography grade): 0.01*M* pH 5.0 phosphate buffer (15:85).

(ii) *Working standard and sample solutions*—(*a*) *Preparation of working standard solution.* Prepare the working standard solution fresh before injection by dissolving an accurately weighed portion of the amdinocillin working standard with sufficient distilled water to obtain a stock solution containing approximately 100 micrograms of amdinocillin per milliliter.

(*b*) *Preparation of sample solutions*—(*1*) *Product not packaged for dispensing (micrograms of amdinocillin per milligram).* Dissolve an accurately weighed portion of the sample with sufficient distilled water to obtain a solution containing 100 micrograms of amdinocillin per milliliter (estimated).

(*2*) *Product packaged for dispensing.* Determine both micrograms of amdinocillin per milligram of the sample and milligrams of amdinocillin per container. Use separate containers for preparation of each sample solution as

described in paragraphs (b)(1)(ii)(*b*)(*2*)(*i*) and (*ii*) of this section.

(*i*) *Micrograms of amdinocillin per milligram.* Dissolve an accurately weighed portion of the sample with sufficient distilled water to obtain a solution containing 100 micrograms of amdinocillin per milliliter (estimated).

(*ii*) *Milligrams of amdinocillin per container.* Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 100 micrograms of amdinocillin per milliliter (estimated).

(*iii*) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 2.5 at 5 percent of peak height:

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,500 theoretical plates.

(*c*) *Resolution factor.* The resolution factor (*R*) between the peak for amdinocillin and its nearest eluting impurity is satisfactory if it is not less than 2.5.

(*d*) *Coefficient of variation.* The coefficient of variation ($S_R$ in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability parameters have been met, then proceed as described in §436.353(b) of this chapter.

(iv) *Calculations.* (*a*) Calculate the micrograms of amdinocillin per milligram of sample as follows:

$$\text{Micrograms of amdinocillin per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - \text{m})}$$

where:

$A_u$=Area of the amdinocillin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the amdinocillin peak in the chromatogram of the amdinocillin working standard;

$P_s$=Amdinocillin activity in the amdinocillin working standard solution in micrograms per milliliter;

$C_u$=Milligrams of sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(*b*) Calculate the amdinocillin content of the container as follows:

$$\text{Milligrams of amdinocillin per container} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Area of the amdinocillin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the amdinocillin peak in the chromatogram of the amdinocillin working standard:

$P_s$=Amdinocillin activity in the amdinocillin working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(a) of this chapter, using a solution containing 40 milligrams of amdinocillin per milliliter.

(4) *Moisture.* Proceed as directed in §436.201 of this chapter.

(5) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams of amdinocillin per milliliter.

(6) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

(7) *Identity.* Proceed as directed in §436.211 of this chapter, using a potassium bromide disc containing 1 milligram of amdinocillin in 300 milligrams of potassium bromide, prepared as described in paragraph (b)(l) of that section.

[50 FR 7765, Feb. 26, 1985; 50 FR 10220, Mar. 14, 1985; 50 FR 18243, Apr. 30, 1985; 55 FR 11582, Mar. 29, 1990]

### §440.3 Amoxicillin trihydrate.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate is the trihydrate form of D(−) $_a$-amino-*p*-hydroxybenzyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms and not more than 1,050

micrograms of amoxicillin per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not less than 11.5 percent and not more than 14.5 percent.

(iv) Its pH in an aqueous solution containing 2 milligrams per milliliter is not less than 3.5 and not more than 6.0.

(v) Its amoxicillin content is not less than 90 percent on an anhydrous basis.

(vi) The acid-base titration concordance is such that the difference between the percent amoxicillin content when determined by nonaqueous acid titration and by nonaqueous base titration is not more than 6. The potency-acid titration concordance is such that the difference between the potency value divided by 10 and the percent amoxicillin content of the sample determined by the nonaqueous acid titration is not more than 6. The potency-base titration concordance is such that the difference between the potency value divided by 10 and the percent amoxicillin content of the sample determined by the nonaqueous base titration is not more than 6.

(vii) It is crystalline.

(viii) It gives a positive identity test for amoxicillin trihydrate.

(2) *Labeling.* In addition to the labeling requirements of §432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the following statement: ''For use in the manufacture of nonparenteral drugs only''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(ii) Samples required: 12 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive:

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution containing 1.0 milligram of amoxicillin per milliliter (estimated). Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 0.1 microgram of amoxicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in §436.201 of this chapter.

(4) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 2 milligrams per milliliter.

(5) *Amoxicillin content.* Proceed as directed in §436.213 of this chapter using both the titration procedures described in paragraphs (e) (1) and (2) of that section. Calculate the percent amoxicillin content as follows:

(i) *Acid titration.*

$$\text{Percent amoxicillin content} = \frac{(A - B)(\text{normality of lithium methoxide reagent})(365.4)(100)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A=Milliliters of lithium methoxide reagent used in titrating the sample.

B=Milliliters of lithium methoxide reagent used in titrating the blank.

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the amoxicillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent amoxicillin content}$$

(ii) *Base titration.*

$$\text{Percent amoxicillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})(365.4)(100)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A=Milliliters of perchloric acid reagent used in titrating the sample.

B=Milliliters of perchloric acid reagent used in titrating the blank.

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the amoxicillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent amoxicillin content}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using a 0.5 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

[39 FR 34032, Sept. 23, 1974, as amended at 46 FR 16682, Mar. 13, 1981; 49 FR 3458, Jan. 27, 1984; 50 FR 19918, May 13, 1985]

### § 440.5 Ampicillin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin is 6-[D-$\alpha$-aminobenzyl] penicillin. It is a white powder. It is so purified and dried that:

(i) It contains not less than 900 micrograms and not more than 1,050 micrograms of ampicillin per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its loss on drying is not more than 2.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.

(v) Its ampicillin content is not less than 90 percent on an anhydrous basis.

(vi) The acid-base titration concordance is such that the difference between the percent ampicillin content when determined by nonaqueous acid titration and by nonaqueous base titration is not more than six. The potency-acid titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous acid titration is not more than six. The potency-base titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous base titration is not more than six.

(vii) It is crystalline.

(viii) It gives a positive identity test for ampicillin.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5(b) of this chapter, each package shall bear on its outside wrapper or container and the immediate container the following statement, ''For use in the manufacture of nonparenteral drugs only''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution containing 0.1 milligram of ampicillin per milliliter (estimated). Further dilute an aliquot of the stock solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Ampicillin content.* Proceed as directed in § 436.213 of this chapter, using both the titration procedures described in paragraphs (e) (1) and (2) of that section. Calculate the percent ampicillin content as follows:

(i) *Acid titration.*

$$\text{Percent ampicillin content} = \frac{(A - B)(\text{normality of lithium methoxide reagent})(349.4)(100)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A=Milliliters of lithium methoxide reagent used in titrating the sample;

B=Milliliters of lithium methoxide reagent used in titrating the blank;

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent ampicillin content}$$

(ii) *Base titration.*

$$\text{Percent ampicillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})(349.4)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A=Milliliters of perchloric acid reagent used in titrating the samples;

B=Milliliters of perchloric acid reagent used in titrating the blank;

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent ampicillin content}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using a 0.5 percent potassium bromide disc, prepared

as described in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 41 FR 42649, Sept. 28, 1976; 46 FR 16682, Mar. 13, 1981; 49 FR 3458, Jan. 27, 1984; 50 FR 19918, May 13, 1985]

### § 440.7 Ampicillin trihydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate is the trihydrate form of D(−)$_a$-amino-benzyl penicillin. It is so purified and dried that:

(i) It contains not less than 900 micrograms and not more than 1,050 micrograms of ampicillin per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its loss on drying is not less than 12 percent and not more than 15 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.

(v) Its ampicillin content is not less than 90 percent on an anhydrous basis.

(vi) The acid-base titration concordance is such that the difference between the percent ampicillin content when determined by nonaqueous acid titration and by nonaqueous base titration is not more than 6. The potency-acid titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous acid titration is not more than 6. The potency-base titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous base titration is not more than 6.

(vii) It is crystalline.

(viii) It gives a positive identity test for ampicillin trihydrate.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5(b) of this chapter, this drug shall be labeled ''ampicillin'' and each package shall bear on its outside wrapper or container and the immediate container the following statement ''For use in the manufacture of nonparenteral drugs only''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(ii) Samples required: 10 packages each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution containing 0.1 milligram of ampicillin per milliliter (estimated). Further dilute an aliquot of the stock solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Ampicillin content.* Proceed as directed in § 436.213 of this chapter, using both the titration procedures described in paragraphs (e) (1) and (2) of that section. Calculate the percent ampicillin content as follows:

(i) *Acid titration.*

Percent ampicillin content=[(A−B) (normality of lithium methoxide reagent) (349.4)

(100) (100)]/[(Weight of sample in milligrams) (100 − *m*)],

where:

A=Milliliters of lithium methoxide reagent used in titrating the sample;

B=Milliliters of lithium methoxide reagent used in titrating the blank;

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

Difference=(Potency in micrograms per milligram/10) − percent ampicillin content.

(ii) *Base titration.*

Percent ampicillin content=[(A − B) (normality of perchloric acid reagent) (349.4) (100) (100)]/[(Weight of sample in milligrams) (100 − *m*)],

where:

A=Milliliters of perchloric acid reagent used in titrating the samples;

B=Milliliters of perchloric acid reagent used in titrating the blank;

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

Difference=(Potency in micrograms per milligram/10) − percent ampicillin content.

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using an 0.5 percent potassium bromide disc, prepared as described in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 46 FR 16683, Mar. 13, 1981; 49 FR 3458, Jan. 27, 1984; 50 FR 19918, May 13, 1985]

### § 440.7a Sterile ampicillin trihydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate is the trihydrate form of D(-)α-aminobenzyl penicillin. It is so purified and dried that:

(i) It contains not less than 900 micrograms and not more than 1,050 micrograms of ampicillin per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not less than 12 percent and not more than 15 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.

(vii) Its ampicillin content is not less than 90 percent on an anhydrous basis.

(viii) The acid-base titration concordance is such that the difference between the percent ampicillin content when determined by nonaqueous acid titration and by nonaqueous base titration is not more than 6. The potency-acid titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous acid titration is not more than 6. The potency-base titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous base titration is not more than 6.

(ix) It is crystalline.

(x) It gives a positive identity test for ampicillin trihydrate.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5(b) of this chapter, this drug shall be labeled ''ampicillin.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive:

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution containing 0.1 milligram of ampicillin per milliliter. Further dilute an aliquot of the stock solution

with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3) to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except in lieu of paragraph (e)(1)(i)(*a*), prepare the sample for test as follows: From each of 10 immediate containers, aseptically transfer approximately 300 milligrams of sample into a sterile 500-milliliter Erlenmeyer flask containing approximately 400 milliliters of diluting fluid D. Add at least 200,000 Levy units[1] of penicillinase. Repeat the process using 10 additional containers. Swirl both of the stoppered flasks to completely solubilize the suspension prior to filtration and proceed as directed in paragraph (e)(1)(ii) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(f) of this chapter, using a solution containing 20 milligrams of ampicillin per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in §436.200(a) of this chapter.

(6) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(7) *Ampicillin content.* Proceed as directed in §436.213 of this chapter, using both the titration procedures described in paragraph (e)(1) and (2) of that section. Calculate the ampicillin content as follows:

(i) *Acid titration.*

Percent ampicillin content=[(A−B) (normality of lithium methoxide reagent) (349.4) (100) (100)]/[(Weight of sample in milligrams) (100−*m*)].

where:
A=Milliliters of lithium methoxide reagent used in titrating the sample;
B=Milliliters of lithium methoxide reagent used in titrating the blank;
*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

Difference=(Potency in micrograms per milligram/10)−percent ampicillin content.

(ii) *Base titration.*

Percent ampicillin content=[(A−B) (normality of perchloric acid reagent) (349.4) (100) (100)]/[(Weight of sample in milligrams) (100−*m*)].

where:
A=Milliliters of perchloric acid reagent used in titrating the samples;
B=Milliliters of perchloric acid reagent used in titrating the blank;
*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

Difference=(Potency in micrograms per milligram/10)−percent ampicillin content.

(8) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

(9) *Identity.* Proceed as directed in §436.211 of this chapter, using a 0.5 percent potassium bromide disc, prepared as described in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 46 FR 16683, Mar. 13, 1981; 49 FR 3458, Jan. 27, 1984; 50 FR 19918, May 13, 1985]

### §440.8 Bacampicillin hydrochloride.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Bacampicillin hydrochloride is the hydrochloride salt of the 1–ethoxycarbonyloxyethyl ester of ampicillin. It is a white powder. It is so purified and dried that:

(i) Its potency is not less than 623 micrograms and not more than 727 micrograms of ampicillin per milligram on an ''as is'' basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 1.0 percent.

(iv) Its pH in an aqueous solution containing 20 milligrams per milliliter

[1] One Levy unit of penicillinase inactivates 59.3 units of penicillin G in 1 hour at 25° C. and at a pH of 7.0 in a phosphate buffered solution of a pure alkali salt of penicillin G when the substrate is in sufficient concentration to maintain a zero order reaction.

is not less than 3.0 and not more than 4.5.

(v) It passes the identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Hydroxylamine colorimetric assay.* Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except:

(*a*) *Buffer.* In lieu of the buffer described in § 442.40(b)(1)(ii) (*b*)(*2*) of this chapter, use the buffer prepared as follows: Dissolve 200 grams of primary standard tris (hydroxymethyl) aminomethane in sufficient distilled water to make 1 liter. Filter before use.

(*b*) *Preparation of working standard solution.* Use the ampicillin working standard. Dissolve and dilute an accurately weighed portion of the ampicillin working standard in sufficient distilled water to obtain a concentration of 1.25 milligrams of ampicillin per milliliter.

(*c*) *Preparation of sample solution.* Dissolve and dilute an accurately weighed portion of the sample with sufficient distilled water to obtain a concentration of 1.25 milligrams of ampicillin per milliliter (estimated).

(*d*) *Calculations.* Calculate the ampicillin content in micrograms per milligram as follows:

$$\text{Ampicillin content in micrograms per milligram} = \frac{A_u \times P_a}{A_s \times W_u}$$

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except use the ampicillin working standard.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 20 milligrams per milliliter.

(5) *Identity.* Proceed as directed in § 436.330 of this chapter.

[46 FR 25603, May 8, 1981, as amended at 50 FR 19918, May 13, 1985]

### § 440.9a Sterile ampicillin sodium.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Sterile ampicillin sodium is the sodium salt of D(-)$_a$-aminobenzyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 845 micrograms and not more than 988 micrograms of ampicillin per milligram on an anhydrous basis. If it is packaged for dispensing, it contains not less than 90 percent and not more than 115 percent of the number of milligrams of ampicillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 2 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 8.0 and not more than 10.0.

(vii) Its ampicillin content is not less than 84.5 percent, except if the high-performance liquid chromatographic (HPLC) assay method is used, then the ampicillin content standard is not applicable.

(viii) The potency-base titration concordance is such that the difference between the potency value divided by 10 and the percent ampicillin content of the sample determined by the nonaqueous base titration is not more than 6, except if the HPLC assay method is used, then the concordance standard is not applicable.

(ix) It is crystalline.

(x) It passes the identity test for ampicillin sodium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, ampicillin content, concordance, crystallinity, and identity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in manufacturing another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 20 packages each containing approximately 300 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers or if each vial contains 250 milligrams or less of ampicillin a minimum of 24 vials.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient sterile distilled water to give a stock solution containing 0.1 milligram of ampicillin per milliliter (estimated), for the microbiological agar diffusion assay and in 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), for the iodometric assay or for the hydroxylamine colorimetric assay to give a stock solution of convenient concentration. For the high-performance liquid chromatographic assay (HPLC), transfer an accurately weighed portion of ampicillin, equivalent to about 100 milligrams of anhydrous ampicillin, to a 100-milliliter volumetric flask. Add about 75 milliliters of diluent (prepared as described in paragraph (b)(1)(ii)(*d*)(*1*)(*ii*) of this section), shake and sonicate, if necessary, to achieve complete dissolution. Also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container, or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with either sterile distilled water, solution 1, or HPLC diluent to give a stock solution as specified above.

(ii) *Assay procedure.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(*d*) *HPLC assay.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a 4-millimeter X 5-centimeter guard column containing 40- to 60-micrometer diameter packing material as described for the analytical column, a 4-millimeter X 30-centimeter analytical column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silica, and a flow rate of about 2.0 milliliters per minute. Separately inject equal volumes (about 20 microliters) of the working standard preparation and the sample solution into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Reagents, working standard and resolution test solution, system suitability requirements, and calculations are as follows:

(*1*) *Reagents*—(*i*) *Mobile phase.* Prepare a suitably filtered and degassed mixture of water, acetonitrile, 1.0*M* monobasic potassium phosphate, and 1.0*N* acetic acid (909:80:10:1).

(*ii*) *Diluent.* Mix 10 milliliters of 1.0*M* monobasic potassium and 1 milliliter of 1.0*N* acetic acid, dilute with water to make 1,000 milliliters, and mix.

(*2*) *Preparation of working and internal standard solutions*—(*i*) *Working standard solution.* Dissolve a portion of ampicillin working standard, accurately weighed, in the diluent to obtain a solution having a known concentration of about 1 milligram per milliliter. Shake and sonicate, if necessary, to achieve complete dissolution. Use this solution promptly after preparation.

(*ii*) *Resolution test solution.* Dissolve caffeine in working standard solution to obtain a solution containing about 1 milligram per milliliter.

(*3*) *System suitability requirements*—(*i*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.4 at 5 percent of peak height.

(*ii*) *Resolution.* The resolution (*R*) between the caffeine and the ampicillin peaks is satisfactory if it is not less than 2.0. The relative retention times are about 2.0 for caffeine and 1.0 for ampicillin.

(*iii*) *Coefficient of variation (relative standard deviation).* The coefficient of variation ($S_R$ in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in §436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are comparable to the system. However, the sample preparation described in paragraph (b)(1)(i) of this section should not be changed.

(*4*) *Calculations.* Calculate the micrograms of ampicillin per milligram of sample as follows:

$$\text{Micrograms of ampicillin per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}$$

where:

$A_u$=Area of the ampicillin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ampicillin peak in the chromatogram of the ampicillin working standard;

$P_s$=Ampicillin activity in the ampicillin working standard solution in micrograms per milliliter;

$C_u$=Milligrams of sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(b) of this chapter, using a solution containing 20 milligrams of ampicillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in §436.201 of this chapter.

(6) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams of ampicillin per milliliter.

(7) *Ampicillin content.* Proceed as directed in §436.213 of this chapter, using the titration procedure described in paragraph (e)(2) of that section. Calculate the ampicillin content as follow

$$\text{Percent ampicillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})(174.7)(100)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A=Milliliters of perchloric acid reagent used in titrating the sample;

B=Milliliters of perchloric acid reagent used in titrating the blank;

*m*=Percent moisture content of the sample.

Calculate the difference between the potency and the ampicillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent ampicillin content}$$

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Identity.* Proceed as directed in § 436.211 of this chapter, using the method described in paragraph (b)(2) of that section.

[39 FR 18976, May 30, 1974, as amended at 41 FR 10886, Mar. 15, 1976; 41 FR 42649, Sept. 28, 1976; 42 FR 59857, Nov. 22, 1977; 46 FR 16683, Mar. 13, 1981; 49 FR 3458, Jan. 27, 1984; 50 FR 19918, May 13, 1985; 52 FR 42288, Nov. 4, 1987; 52 FR 45281, Nov. 25, 1987; 54 FR 47204, Nov. 13, 1989]

### § 440.10 Benzylpenicilloyl-polylysine concentrate.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Benzylpenicilloyl-polylysine concentrate is a pale yellow to dark yellow aqueous solution of benzylpenicilloyl *e* substituted poly-L-lysine. It contains one or more suitable and harmless buffers. It is so purified that:

(i) It contains not less than 50 percent and not more than 70 percent benzylpenicilloyl substitution on the polylysine.

(ii) The benzylpenicilloyl concentration is not less than $1.25\times10^{-2}M$ and not more than $2.0\times10^{-2}M$.

(iii) The penamaldate concentration is not more than $6.0\times10^{-4}M$.

(iv) The penicillenate concentration is not more than $2.0\times10^{-4}M$.

(v) Its pH is not less than 6.5 and not more than 8.5.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for percent benzylpenicilloyl substitution, benzylpenicilloyl content, penamaldate content, penicillenate content, and pH.

(ii) Samples required: 2 vials, each containing not less than 5 milliliters.

(b) *Tests and methods of assay*—(1) *Percent benzylpenicilloyl substitution*—(i) *Lysine content*—(*a*) *Equipment.* Amino acid analyzer capable of:

(*1*) Separating the hydrolysis products of benzylpenicilloyl polylysine into discrete components by means of an ion-exchange column.

(*2*) Mixing the separated amino acid components with a ninhydrin reagent and promoting the reaction in a coil at elevated temperatures.

(*3*) Quantitating the ninhydrin positive materials by means of a suitable colorimeter and recorder.

(*b*) *Reagents*—(*1*) Citrate buffer: Dissolve and dilute 19.69 grams of sodium citrate dihydrate, 16.5 milliliters of hydrochloric acid, 0.1 milliliter of pentachlorophenol, 5 milliliters of thiodiglycol in 900 milliliters of distilled water; adjust to a pH of 2.2 and dilute to 1 liter with distilled water.

(*2*) Calibration mixture: Dissolve and dilute equal molar amounts of ammonia, and the L form of lysine in the citrate buffer to result in final concentrations of $2.5\times10^{-4}M$ for each.

(*c*) *Preparation of standard and sample solutions*—(*1*) *Standard solution* (*standard lysine solution* ($2.5\times10^{-4}$ *M*)). Transfer an accurately weighed portion of 54.8 milligrams of lysine dihydrochloride to a 100-milliliter volumetric flask. Dissolve and dilute to mark with citrate buffer. Make an accurate tenfold dilution of this solution with citrate buffer. The resulting standard solution is $2.5\times10^{-4}$ *M* with respect to lysine.

(*2*) *Sample solution.* Dilute 1 milliliter of the benzylpenicilloyl-polylysine concentrate to 10 milliliters with distilled water. Mix 1 milliliter of the diluted solution with 1.5 milliliters of 6.0*N* hydrochloric acid and seal in an ampule under nitrogen. Hydrolyze the solution for 22 hours at 110° C. Transfer the contents of the ampule quantitatively into a 50-milliliter round bottom flask and dry by rotary evaporation. Wash the contents and evaporate to dryness three times using 5-milliliter portions of distilled water. Dissolve the hydrolysate in 10 milliliters of citrate buffer.

(*d*) *Procedure.* Standardize the procedure for use of the amino acid analyzer with the calibration mixture. Apply 0.5 milliliter of the lysine standard solution to the amino acid analyzer and determine the area of the lysine peak. Apply 0.5 milliliter of the sample solution to the amino acid analyzer and determine the area of the lysine peak.

(*e*) *Calculations.* Calculate the lysine content by the following formula:

$$\text{Molar concentration of lysine in the benzylpenicilloyl-polylysine concentrate} = \frac{A \times 2.5}{B \times C}$$

where:

*A*=The area of the lysine peak of the sample solution.

*B*=The area of the lysine peak of the standard solution.

*C*=The percent purity of the lysine dihydrochloride.

(ii) *Benzylpenicilloyl content*—(*a*) *Reagents.* (*1*) Mercuric chloride solution: Dissolve 35 milligrams of mercuric chloride in 500 milliliters of distilled water.

(*2*) Saline phosphate buffer, pH 7.6: Dissolve 9 grams of sodium chloride and 1.38 grams monobasic sodium phosphate in 900 milliliters of distilled water, adjust to pH 7.6 and dilute to 1 liter with distilled water.

(*b*) *Preparation of sample solution.* Transfer 1 milliliter of the benzylpenicilloyl-polylysine concentrate into a 500-milliliter volumetric flask and dilute to volume with saline phosphate buffer, pH 7.6.

(*c*) *Procedure.* Transfer 3 milliliters of the sample solution into a spectrophotometric cell. Using a suitable spectrophotometer and the saline phosphate buffer, pH 7.6, as a blank, determine the initial absorbance at 282 nanometers. Thereafter, react the diluted benzylpenicilloyl-polylysine solution with 0.02-milliliter portions of the mercuric chloride solution. Determine the absorbance at 282 nanometers at 1 and 3 minutes after each addition of mercuric chloride solution. The increased absorbance at 282 nanometers is used in calculating the benzylpenicilloyl content. Calculate the benzylpenicilloyl content by means of the following formula:

$$\text{Molar benzylpenicilloyl content} = \frac{(A_1 - A_2) \times 500}{22{,}325}$$

where:

$A_1$=The highest absorbance at 282 nanometers

$A_2$=The initial absorbance at 282 nanometers

22,325=The molar absorptivity of the penamaldate formed by the reaction of the benzylpenicilloyl moiety with the mercuric chloride at a pH of 7.6.

Percent benzylpenicilloyl substitution=(Molar benzylpenicilloyl content $\times$100)/Molar lysine content

(2) *Penicillenate and penamaldate content.* Dilute 1 milliliter of the benzylpenicilloyl-polylysine concentrate to 50 milliliters with saline phosphate buffer, pH 7.6. Using a suitable spectrophotometer and the saline phosphate buffer, pH 7.6, as a blank, determine the absorbance at 322 and 282 nanometers. Calculate the penicillenate content by the following formula:

$$\text{Molar penicillenate content} = \frac{\text{Absorbance at 322 nanometers} \times 50}{26{,}600}$$

where:

26,600=Molar absorptivity of the penicillenate moiety at 322 nanometers at a pH of 7.6

Calculate the penamaldate content by the following formula:

$$\text{Molar penamaldate content} = \frac{\text{Absorbance at 282 nanometers} \times 50}{22{,}325}$$

where:

22,325=Molar absorptivity of the penamaldate moiety at 282 nanometers at a pH of 7.6.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the undiluted sample.

[39 FR 35346, Oct. 1, 1974; 39 FR 38370, Oct. 31, 1974; 39 FR 39871, Nov. 12, 1974; 39 FR 40946, Nov. 22, 1974]

### § 440.11 Carbenicillin indanyl sodium.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Carbenicillin indanyl sodium is the monosodium salt of *N*-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-

azabicyclo [3.2.0] hept-6-yl)-2-phenylmalonamic acid, 1-(5-indanyl) ester. It is so purified and dried that:

(i) Its potency is not less than 659 micrograms and not more than 769 micrograms of carbenicillin per milligram on an anhydrous basis at the time of certification, and not less than 630 micrograms of carbenicillin per milligram on an anhydrous basis at any time during the expiration period.

(ii) [Reserved]

(iii) Its moisture content is not more than 2.0 percent.

(iv) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 5.0 nor more than 8.0.

(v) It gives a positive result to the identity test for carbenicillin indanyl sodium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, and identity.

(ii) Samples required: Five packages, each containing approximately 1.0 gram and one package containing approximately 2.5 grams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.300 of this chapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in §436.201 of this chapter.

(4) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(5) *Identity.* Proceed as directed in §436.211 of this chapter, using the 0.5-percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 50 FR 19918, May 13, 1985]

### §440.13a Sterile carbenicillin disodium.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Carbenicillin disodium is the disodium salt of α-carboxybenzylpenicillin. It is so purified and dried that:

(i) It contains not less than 770 micrograms of carbenicillin per milligram on an anhydrous basis. If it is packaged for dispensing, its carbenicillin content is not less than 90 percent and not more than 120 percent of the number of milligrams of carbenicillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 6 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams of carbenicillin per milliliter (or if packaged for dispensing, after reconstitution as directed in the labeling) is not less than 6.0 and not more than 8.0.

(vii) It gives a positive identity test for carbenicillin disodium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution

of convenient concentration; and also if it is packaged for dispensing, reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single–dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. If it is a single dose container, use a separate needle and syringe for each container. Dilute with sufficient solution 1 to give a stock solution of convenient concentration. Further dilute the stock solution with solution 1 to the reference concentration of 20.0 micrograms of carbenicillin per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 200 milligrams of carbenicillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams of carbenicillin per milliliter (or if packaged for dispensing, use a solution prepared as directed for reconstitution in the labeling).

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using a 0.5 percent potassium bromide disc prepared as directed in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 45 FR 22921, Apr. 4, 1980; 50 FR 19918, May 13, 1985; 51 FR 27532, Aug. 1, 1986]

### § 440.15 Cloxacillin sodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cloxacillin sodium is the monohydrate sodium salt of 5-methyl-3-(*o*- chlorophenyl)-4-isoxazolyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 825 micrograms of cloxacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3 percent and not more than 5 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.5 nor more than 7.5.

(v) Its cloxacillin content is not less than 82.5 percent.

(vi) It passes the identity test.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this subchapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, cloxacillin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of cloxacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this subchapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this subchapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this subchapter.

(4) *pH.* Proceed as directed in § 436.202 of this subchapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Cloxacillin content.* Accurately weigh approximately 100 milligrams of the sample and dissolve in sufficient 5*N* sodium hydroxide to give a total volume of 25 milliliters. Place in a boiling water bath for 30 minutes. Cool, acidify 1 milliliter with 1 milliliter of dilute sulfuric acid (1 in 2), add 8 milliliters of water, and extract with two 25-milliliter portions of ethyl ether. Combine the ether extractives and extract with 25-milliliter portions of 0.1*N* sodium hydroxide. Combine the alkaline extractives and dilute to 100 milliliters with carbon dioxide-free water. Treat a portion of the cloxacillin working standard in the same manner. Using a suitable spectrophotometer, determine the absorbance of the solution in a 1-centimeter cell at the absorption peaks at 257±3 nanometers and at 282±3 nanometers compared with a reagent blank. Determine the percent cloxacillin in the sample by means of the following calculation:

$$\text{Percent cloxacillin} = \frac{A_1 \times \text{weight of standard in milligrams, on an "as is" basis} \times \text{percent cloxacillin in the standard}}{A_2 \times \text{weight of sample in milligrams on an "as is" basis} \times 100}$$

where:

$A_1$=Difference in absorbance for the sample between 257 nanometers and 282 nanometers:

$A_2$=Difference in absorbance for the cloxacillin working standard, similarly treated.

(6) *Identity.* Proceed as directed in § 436.211 of this subchapter, using the 0.5 percent potassium bromide disc described in paragraph (b)(1) of that section.

(7) *Crystallinity.* Proceed as directed in § 436.203 of this subchapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 50 FR 19918, May 13, 1985]

### § 440.17 Cyclacillin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cyclacillin is 6-(1-aminocyclohexanecarboxamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid. It is a white to off-white powder. It is so purified and dried that:

(i) It contains not less than 900 micrograms and not more than 1,050 micrograms of cyclacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 1.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.0 and not more than 6.5.

(v) Its cyclacillin content is not less than 90 percent on an anhydrous basis.

(vi) The acid-base titration concordance is such that the difference between the percent cyclacillin content when determined by nonaqueous acid titration and nonaqueous base titration is not more than six. The potency-acid titration concordance is such that the difference between the potency value divided by 10 and the percent cyclacillin content of the sample determined by the nonaqueous acid titration is not more than six. The potency base titration concordance is such that the difference between the potency value divided by 10 and the percent cyclacillin content of the sample determined by the nonaqueous base titration is not more than six.

(vii) It is crystalline.

(viii) It gives a positive identity test for cyclacillin.

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the following statement, ''For use in the manufacture of nonparenteral drugs only.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, cyclacillin content, concordance, crystallinity, and identity.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution containing 1 milligram of cyclacillin per milliliter (estimated). Further dilute an aliquot of the stock solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of cyclacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Cyclacillin content.* Proceed as directed in § 436.213 of this chapter, using both the titration procedures described in paragraph (e)(1) and (2) of that section. Calculate the percent cyclacillin content as follows:

(i) *Acid titration.*

$$\text{Percent cyclacillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})(341.4)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A = Milliliters of lithium methoxide reagent used in titrating the sample;

B = Milliliters of lithium methoxide reagent used in titrating the blank;

*m* = Percent moisture content of the sample.

Calculate the difference between the potency and the cyclacillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent cyclacillin content}$$

(ii) *Base titration.*

$$\text{Percent cyclacillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})\,(341.4)(100)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A = Milliliters of perchloric acid reagent used in titrating the sample;

B = Milliliters of perchloric acid reagent used in titrating the blank;

*m* = Percent moisture content of the sample.

Calculate the difference between the potency and the cyclacillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligrams}}{10} - \text{percent cyclacillin content}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using a 1-percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

[46 FR 2981, Jan. 13, 1981; 46 FR 15880, Mar. 10, 1981, as amended at 50 FR 19918, May 13, 1985]

### § 440.19 Dicloxacillin sodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Dicloxacillin sodium monohydrate is the monohydrated sodium salt of 5-methyl-3-(2,6-dichlorophenyl)-4-isoxazolyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 850 micrograms of dicloxacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3 percent nor more than 5 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.5 nor more than 7.5.

(v) Its organic chlorine content is not less than 13.0 percent nor more than 14.2 percent.

(vi) Its free chloride content is not more than 0.5 percent.

(vii) It is crystalline.

(viii) It gives a positive identity test for dicloxacillin sodium monohydrate.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, organic chlorine content, free chloride content, crystallinity, and identity.

(ii) Samples required: 10 containers, each containing not less than 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay, as follows: Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of dicloxacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Moisture content.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Organic chlorine content*—(i) *Reagents. (a) o-* Chlorobenzoic acid of known purity.

(*b*) 0.01*N* Silver nitrate solution. Store in brown glass reagent bottle. Standardize against an accurately weighed sample of 20 to 25 milligrams of *o-* chlorobenzoic acid using the procedure described in paragraph (b)(5)(ii) of this section.

$$\text{Normality } (N) = \frac{\text{Percent purity of the } o\text{-chlorobenzoic acid} \times \text{milligrams of } o\text{-chlorobenzoic acid}}{15{,}657 \times \text{milliliters of silver nitrate consumed}}$$

(*c*) 0.1*N* Sodium hydroxide solution.

(*d*) 1:1 Nitric acid solution: Mix 1 volume of concentrated nitric acid with 1 volume of distilled water.

(ii) *Total chlorine.* (Caution—The analyst should wear safety glasses and use a suitable shield between himself and the apparatus. The glassware must be scrupulously clean.) Accurately weigh

20 to 25 milligrams of the sample and place it on the center of a piece of halide-free filter paper measuring about 4 centimeters square (this is specially cut paper with a fuse strip attached to the area that holds the sample), and fold the paper to enclose it. Place 10 milliliters of 0.1*N* sodium hydroxide into an oxygen combustion flask (Schoniger flask), and flush the air from the flask with a stream of rapidly flowing oxygen. Place the sample into the platinum sample holder and ignite the fuse strip by suitable means. If the strip is ignited outside the flask, immediately plunge the stopper into the flask, invert so that the sodium hydroxide solution makes a seal around the stopper, and hold the stopper firmly in place. If the ignition is carried out in a closed system, the inversion of the flask may be omitted. After combustion is completed, shake the flask vigorously, add a small amount of distilled water to the collar to insure an air tight seal, and allow to stand for not less than 10 minutes with intermittent shaking. Transfer to a suitable titration vessel, heat on a steam bath for 20 to 30 minutes, cool to room temperature, add 5 milliliters of nitric acid solution, and titrate potentiometrically with 0.01*N* silver nitrate, using one silver electrode and one silver/silver chloride electrode.

$$\text{Percent total chlorine} = \frac{N \times \text{milliliters of silver nitrate} \times 3545.7}{\text{Milligrams of sample}}$$

(iii) *Free chloride.* Accurately weigh 100 to 150 milligrams of sample directly into a titration flask, dissolve in 10 milliliters of 0.1*N* sodium hydroxide, and add about 20 milliliters of distilled water, heat this solution on the steam bath 20 to 30 minutes. Cool to room temperature, add 5 milliliters of 1:1 nitric acid solution and titrate potentiometrically with 0.01*N* silver nitrate using one silver electrode and one silver/silver chloride electrode.

$$\text{Percent free chloride} = \frac{N \times \text{milliliters of silver nitrate} \times 3545.7}{\text{Milligrams of sample}}$$

(iv) *Organic chlorine.* Percent organic chlorine=Percent total chlorine − percent free chloride.

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using the 1 percent potassium bromide disc described in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 44 FR 10378, Feb. 20, 1979; 50 FR 19918, May 13, 1985]

### § 440.19a Sterile dicloxacillin sodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile dicloxacillin sodium monohydrate is the monohydrated sodium salt of 5-methyl-3-(2,6-dichlorophenyl)-4-isoxazolyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 850 micrograms of dicloxacillin per milligram. If it is packaged for dispensing, its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of dicloxacillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 3 percent and not more than 5 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter

or when reconstituted as directed in the labeling, if it is packaged for dispensing is not less than 4.5 nor more than 7.5.

(vii) Its organic chlorine content is not less than 13.0 percent and not more than 14.2 percent.

(viii) Its free chloride content is not more than 0.5 percent.

(ix) It is crystalline.

(x) It gives a positive identity test for dicloxacillin sodium monohydrate.

(2) *Labeling.* If this drug is packaged for dispensing, in addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''sterile dicloxacillin sodium''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, organic chlorine content, free chloride content, crystallinity, and identity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Sample preparation*. Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay and the hydroxylamine colorimetric assay or in distilled water for the iodometric assay, to give a stock solution of convenient concentration; and also if it is packaged for dispensing, reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container, or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with either solution 1 or distilled water, as specified above, to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

*(a) Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of dicloxacillin per milliliter (estimated).

(*b*) *Iodometric assay*. Proceed as directed in § 436.204 of this subchapter.

(*c*) *Hydroxylamine colorimetric assay*. Proceed as directed in § 436.205 of this subchapter.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 20 milligrams of dicloxacillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH*. Proceed as directed in § 436.202 of this subchapter, using an aqueous solution containing 10 milligrams per milliliter (or using a solution reconstituted as directed in the labeling if it is packaged for dispensing).

(7) *Organic chlorine content.* Proceed as directed in § 440.19(b)(5).

(8) *Crystallinity*. Proceed as directed in § 436.203(a) of this chapter.

(9) *Identity*. Proceed as directed in § 436.211 of this chapter, using a 1 percent potassium bromide disc prepared as directed in paragraph (b)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 50 FR 19918, May 13, 1985]

**§ 440.25 Hetacillin.**

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Hetacillin is 6-(2,2-Dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It occurs as a fine, white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 810 micrograms of ampicillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 1.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.5 nor more than 5.5.

(v) Its hetacillin content is not less than 90 and not more than 105 percent.

(vi) It gives a positive identity test for hetacillin.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed for ampicillin in § 436.105 of this chapter, using the ampicillin working standard as the standard of comparison and preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Further dilute the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Hetacillin content*—(i) *Reagents—(a) Hydrochloric acid-acetone solution.* Dilute 8.5 milliliters of concentrated hydrochloric acid to 1 liter with acetone and mix well. Use for 1 day only.

(*b*) *p-Dimethylaminocinnamalde- hyde solution.* Dissolve 0.5 gram of *p*-dimethylaminocinnamaldehyde in sufficient hydrochloric acid-acetone solution to a final volume of 100 milliliters and shake well, filtering if necessary. Prepare immediately before use.

(ii) *Preparation of standard solutions.* Transfer about 100 milligrams of the hetacillin working standard, accurately weighed, to a 200-milliliter volumetric flask. Add 150 milliliters of refrigerated distilled water and 20 milliliters of 1*N* hydrochloric acid, shake, dilute to volume with distilled water, and mix well. Transfer 0.5, 1.0, and 2.0 milliliters into three respective 25-milliliter volumetric flasks. Add 1.5 and 1.0 milliliters of 0.1*N* hydrochloric acid respectively to the first and second flasks to bring the volume in each to 2.0 milliliters.

(iii) *Blank.* Use 2.0 milliliters of 0.1*N* hydrochloric acid in a 25-milliliter volumetric flask.

(iv) *Preparation of sample solutions.* Using a mortar and pestle, grind the sample to a fine powder. Transfer an accurately weighed portion of about 100 milligrams to a 200-milliliter volumetric flask. Add 150 milliliters of refrigerated distilled water and 20 milliliters of 1*N* hydrochloric acid, shake, dilute to volume with distilled water, and mix well. Transfer 1.0 milliliter to a 25-milliliter volumetric flask, add 1.0 milliliter of 0.1*N* hydrochloric acid, and mix.

(v) *Procedure.* To each of the flasks containing standards, blank, and sample, add 15 milliliters of hydrochloric acid-acetone solution and mix. Then add 3 milliliters of *p*- dimethylaminocinnamaldehyde solution to each and mix. Add 3 milliliters of 0.1*N* hydrochloric acid to each, dilute to volume with hydrochloric acid-acetone solution, mix well, and allow to stand at 25° C. for exactly 30 minutes. (Filter the sample solutions, if necessary, to remove any turbidity.) Using a suitable spectrophotometer, read the absorbance values of standard and sample solutions at a wavelength of 515

nanometers against the blank. Plot the absorbance values of the standards versus their concentrations and read the sample concentration from this standard response line.

(vi) *Calculations.*

$$\text{Percent hetacillin} = \frac{C \times 5{,}000 \times P}{\text{Weight of sample in milligrams}}$$

where:

*C*=Concentration in milligrams of hetacillin per milliliter of the final solution of the sample obtained from the standard response line.

*P*=Hetacillin content of the hetacillin working standard in percent.

(6) *Identity.* Proceed as directed in §436.211 of this chapter, using a 1 percent potassium bromide disc prepared as directed in paragraph (b)(1) of that section.

(7) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 44 FR 10379, Feb. 20, 1979; 50 FR 19918, May 13, 1985]

### §440.29 Hetacillin potassium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality and purity.* Hetacillin potassium is the potassium salt of hetacillin. It occurs as a fine, white to light buff powder. It is so purified and dried that:

(i) Its potency is not less than 735 micrograms of ampicillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 1.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 7.0 and not more than 9.0.

(v) Its hetacillin content is not less than 82 percent and not more than 95.5 percent.

(vi) It gives a positive identity test for hetacillin potassium.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed for ampicillin in §436.105 of this chapter, using the ampicillin working standard as the standard of comparison and preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 0.1*M* potassium phosphate buffer pH 8.0 (solution 3), to give a stock solution of convenient concentration. Further dilute the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) [Reserved]

(3) *Moisture.* Proceed as directed in §436.201 of this chapter.

(4) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Hetacillin content.* Proceed as directed in §440.25(b)(5), except use about 110 milligrams of sample and calculate the hetacillin content as follows:

$$\text{Percent hetacillin} = \frac{C \times 5{,}000 \times P}{\text{Weight of sample in milligrams}}$$

where:

*C*=Concentration in milligrams of hetacillin per milliliter of the final solution of the sample obtained from the standard response line.

*P*=Hetacillin content of the hetacillin working standard in percent.

(6) *Identity.* Proceed as directed in §436.211 of this chapter, using a 1 percent potassium bromide disc prepared as directed in paragraph (b)(1) of that section.

(7) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 44 FR 10379, Feb. 20, 1979; 50 FR 19918, May 13, 1985]

### §440.29a Sterile hetacillin potassium.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Hetacillin potassium is the

potassium salt of hetacillin. It occurs as a fine, white to light buff powder. It is so purified and dried that:

(i) Its potency is not less than 735 micrograms of ampicillin per milligram. If it is packaged for dispensing, its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 1.0 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter (or when reconstituted as directed in the labeling, if it is packaged for dispensing) is not less than 7.0 and not more than 9.0.

(vii) Its hetacillin content is not less than 82 percent and not more than 95.5 percent.

(viii) It gives a positive identity test for hetacillin potassium.

(ix) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, hetacillin content, identity, and crystallinity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers, except if each contains less than 450 milligrams, a minimum of 16 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed for ampicillin in §436.105 of this chapter, using the ampicillin working standard as the standard of comparison and preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration; and also if it is packaged for dispensing, reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove the withdrawable contents from each container represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, withdraw an accurately measured representative portion from each container. Dilute the sample thus obtained with sufficient solution 3 to give a stock solution of convenient concentration. Further dilute the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(a) of this chapter using a solution containing the equivalent of 18 milligrams of ampicillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in §436.201 of this chapter.

(6) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter (or using a solution reconstituted as directed in the labeling, if it is packaged for dispensing).

(7) *Hetacillin content.* Proceed as directed in §440.25(b)(5), except use about 110 milligrams of sample and calculate the potassium hetacillin content as follows:

$$\text{Percent hetacillin} = \frac{C \times 5{,}000 \times P}{\text{Weight of sample in milligrams}}$$

where:

*C*=Concentration in milligrams of hetacillin per milliliter of the final solution of the sample obtained from the standard response line.

*P*=Hetacillin content of the hetacillin working standard in percent.

(8) *Identity.* Proceed as directed in § 436.211 of this chapter, using a 1 percent potassium bromide disc prepared as directed in paragraph (b)(1) of that section.

(9) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[39 FR 19876, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 43 FR 2393, Jan. 17, 1978; 44 FR 10379, Feb. 20, 1979; 50 FR 19918, May 13, 1985]

### § 440.36a Sterile methicillin sodium monohydrate.

(a) *Requirements for certification—* (1) *Standards of identity, strength, quality, and purity.* Methicillin sodium monohydrate is the monohydrated sodium salt of (2,6-dimethoxyphenyl) penicillin. It is so purified and dried that:

(i) It contains not less than 815 micrograms of methicillin per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 3 percent and not more than 6 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(vii) Its methicillin content is not less than 81.5 percent.

(viii) It is crystalline.

(ix) It passes the identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this subchapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, methicillin content, crystallinity, and identity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams, plus one package containing approximately 2 grams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay—*(1) *Potency.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 10 micrograms of methicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this subchapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this subchapter.

(2) *Sterility.* Proceed as directed in in § 436.20 of this subchapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 60 milligrams of methicillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this subchapter.

(6) *pH.* Proceed as directed in § 436.202 of this subchapter, using an aqueous solution containing 10 milligrams per milliliter.

(7) *Methicillin content.* Dissolve an accurately weighed portion of the sample in a sufficient accurately measured volume of distilled water to obtain a concentration of 0.2 milligram of methicillin per milliliter (estimated). Treat a portion of the methicillin working standard in the same manner. Using a suitable spectrophotometer equipped with a 1-centimeter quartz cell and distilled water as the blank,

determine the absorbance at 280 nanometers. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 250 nanometers to 300 nanometers. If a nonrecording spectrophotometer is used, determine the absorbance (on a solution containing 10 milligrams per 100 milliliters) at the 280-nanometer absorption peak. (The exact position of the peak should be determined for the particular instrument used.) Calculate as follows:

$$\text{Percent methicillin} = \frac{\text{Absorbance of sample} \times \text{weight of working standard} \times \text{volume of sample solution} \times \text{percent methicillin in working standard}}{\text{Absorbance of standard} \times \text{weight of sample} \times \text{volume of standard solution}}$$

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this subchapter.

(9) *Identity.* Using the sample solution prepared as described in paragraph (b)(7) of this section, determine the absorbancies at the absorption maximum at 280 nanometers and at the absorption minimum at 264 nanometers. The ratio of the two

$$A_{280}/A_{264}$$

should be not less than 1.30 and not more than 1.45.

[39 FR 18976, May 30, 1974, as amended at 40 FR 15089, Apr. 4, 1975; 42 FR 59858, Nov. 22, 1977; 50 FR 19918, May 13, 1985]

### § 440.37a Sterile mezlocillin sodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile mezlocillin sodium monohydrate is the monohydrate sodium salt of (2*S*, 5*R*, 6*R*)-3,3-dimethyl-6-[(*R*)-2-[3-(methylsulfonyl)-2-oxo-1-imidazolidine-carboxamido]-2-phenylacetamido]-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid. It is so purified and dried that:

(i) It contains not less than 838 micrograms and not more than 978 micrograms of mezlocillin per milligram on an anhydrous basis. If it is packaged for dispensing, its mezlocillin content is not less than 90 percent and not more than 115 percent of the number of milligrams of mezlocillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 6.0 percent.

(vi) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 4.5 and not more than 8.0.

(vii) The specific rotation in an aqueous solution containing 10 milligrams of mezlocillin per milliliter at 25° C is 185°±10°.

(viii) It gives a positive identity test for mezlocillin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, specific rotation, and identity.

(ii) Samples required:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric assay shall be conclusive.

(i) *Hydroxylamine colorimetric assay*. Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except:

(*a*) *Buffer.* In lieu of the buffer described in § 442.40(b)(1)(ii)(*b*)(*2*) of this chapter, use the buffer prepared as follows: Dissolve 200 grams of primary standard tris (hydroxymethyl) aminomethane in sufficient distilled water to make 1 liter. Filter before use.

(*b*) *Preparation of working standard solution*. Dissolve and dilute an accurately weighed portion of the mezlocillin working standard with sufficient distilled water to obtain a concentration of 2.0 milligrams of mezlocillin per milliliter.

(*c*) *Preparation of sample solution*. Dissolve an accurately weighed portion of the sample with sufficient distilled water to obtain a stock solution of convenient concentration; also, if packaged for dispensing, reconstitute as directed in the labeling using distilled water in lieu of the reconstituting fluid. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to a concentration of 2.0 milligrams of mezlocillin per milliliter (estimated).

(*d*) *Calculations*—(*1*) Calculate the mezlocillin content in micrograms per milligram as follows:

$$\text{Micrograms of mezlocillin per milligram of sample} = \frac{A_u \times P_a}{A_s \times W_u}$$

where:

$A_u$=Absorbance of sample solution;
$P_a$=Potency of working standard solution in micrograms per milliliter;
$A_s$=Absorbance of working standard solution;
$W_u$=Milligrams of sample per milliliter of sample solution.

(*2*) Calculate the mezlocillin content of the single-dose vial as follows:

$$\text{Milligrams of mezlocillin per single-dose vial} = \frac{A_u \times P_a \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Absorbance of sample solution;
$P_a$=Potency of working standard solution in micrograms per milliliter;
$A_s$=Absorbance of working standard solution;
$d$=Dilution factor of the sample.

(*3*) Calculate the mezlocillin content of the multiple-dose vial as follows:

$$\text{Milligrams of mezlocillin per multiple-dose vial} = \frac{A_u \times P_a \times d}{A_s \times 1{,}000 \times n}$$

where:

$A_u$=Absorbance of sample solution;
$P_a$=Potency of working standard solution in micrograms per milliliter;
$A_s$=Absorbance of working standard solution;
$d$=Dilution factor of the sample;
$n$=Volume of sample solution assayed.

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 100 milligrams of mezlocillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams of mezlocillin per milliliter.

(7) *Specific rotation*. Dilute an accurately weighed sample with sufficient distilled water to obtain a concentration of approximately 10 milligrams of mezlocillin per milliliter. Proceed as directed in § 436.210 of this chapter, using a 1-decimeter polarimeter tube.

(8) *Identity*. Proceed as directed in § 436.311 of this chapter, diluting the sample with distilled water to a concentration of 4 milligrams of mezlocillin per milliliter, except:

(i) Use the mezlocillin working standard and dilute with distilled water to a concentration of 4 milligrams of mezlocillin per milligram;

(ii) In lieu of the ninhydrin spray solution, after the plate is dried with a current of warm air, expose the plate to iodine vapors for about 30 seconds; and

(iii) Mezlocillin has an $R_f$ value of about 0.67.

[46 FR 58298, Dec. 1, 1981, as amended at 50 FR 19918, 19919, May 13, 1985]

### § 440.41 Nafcillin sodium monohydrate.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Nafcillin sodium monohydrate is the monohydrated sodium salt of 6-(2-ethoxy-1-naphthamido) penicillanic acid. It is so purified and dried that:

(i) It contains not less than 820 micrograms of nafcillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3.5 percent and not more than 5.3 percent.

(iv) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 5.0 and not more than 7.0.

(v) It is crystalline.

(vi) Its nafcillin content is not less than 82.0 percent.

(vii) It gives a positive identity test for nafcillin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods: however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 2 micrograms of nafcillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 30 milligrams per milliliter.

(5) *Crystallinity.* Proceed as directed in § 436.203(b) of this chapter.

(6) *Nafcillin content.* Dissolve an accurately weighed portion of the sample in a sufficient accurately measured volume of distilled water to obtain a concentration of 0.05 milligram of nafcillin per milliliter (estimated). Treat a portion of the nafcillin working standard in the same manner. Using a suitable spectrophotometer equipped with quartz cells and distilled water as a blank, scan the absorption spectra of the sample and the nafcillin working standard solutions between the wavelengths of 245 nanometers and 340 nanometers. Determine the absorbance of the sample and working standard solutions at the absorption maximum at 280±3 nanometers. (The exact position of the maximum should be determined for the particular instrument used.) Calculate as follows:

$$\text{Percent nafcillin} = \frac{\text{Absorbance of sample} \times \text{weight in milligrams of standard} \times \text{volume of sample solution} \times \text{nafcillin content of standard in percent}}{\text{Absorbance of standard} \times \text{weight in milligrams of sample} \times \text{volume of standard solution}}$$

(7) *Identity.* The absorption spectrum of the sample determined as directed in paragraph (b)(6) of this section compares qualitatively with that of the nafcillin working standard.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59858, Nov. 22, 1977; 46 FR 16683, Mar. 13, 1981; 50 FR 19918, 19919, May 13, 1985]

### § 440.41a Sterile nafcillin sodium monohydrate.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Sterile nafcillin sodium monohydrate is the monohydrated sodium salt of 6-(2-ethoxy-1-naphthamido) penicillanic acid. It is so purified and dried that:

(i) It contains not less than 820 micrograms of nafcillin per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 3.5 nor more than 5.3 percent.

(vi) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 5.0 and not more than 7.0.

(vii) It is crystalline.

(viii) Its nafcillin content is not less than 82.0 percent.

(ix) It gives a positive identity test for nafcillin.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, crystallinity, nafcillin content, and identity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods: however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 2 micrograms of nafcillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 80 milligrams of nafcillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 30 milligrams per milliliter.

(7) *Crystallinity.* Proceed as directed in § 436.203(b) of this chapter.

(8) *Nafcillin content.* Proceed as directed in § 440.41(b)(6).

(9) *Identity.* The absorption spectrum of the sample determined as directed in

paragraph (b)(8) of this section compares qualitatively with that of the nafcillin working standard.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59858, Nov. 22, 1977; 45 FR 16474, Mar. 14, 1980; 45 FR 22921, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### § 440.49 Oxacillin sodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxacillin sodium monohydrate is the monohydrated sodium salt of 5-methyl-3-phenyl-4-isoxazolyl penicillin. It is so purified and dried that:

(i) It contains not less than 815 and not more than 950 micrograms of oxacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3.5 and not more than 5.0 percent.

(iv) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 4.5 and not more than 7.5.

(v) Its oxacillin content is not less than 81.5 percent and not more than 95.0 percent.

(vi) It is crystalline.

(vii) It gives a positive identity test for the oxacillin moiety.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, oxacillin content, crystallinity, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5.0 micrograms of oxacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a solution containing 30 milligrams per milliliter.

(5) *Oxacillin content.* Place approximately 60 milligrams of sample, accurately weighed, into a 100-milliliter volumetric flask. Dissolve and fill to volume with distilled water. Pipette a 5.0-milliliter aliquot of the sample solution into a 22- by 200-millimeter test tube, and add 5 milliliters of 10 *N* NaOH. Mix the solution, and place the tube in a boiling water bath for 60 minutes. Cool the tube, carefully add 10 milliliters of 6 *N* HCl, mix, and replace the tube in the boiling water bath for 10 minutes. Position the tube in the bath so that the liquid level in the tube is the same as the liquid level in the bath. After heating, remove the tube from the bath, carefully agitate the contents of the tube, and cool to room temperature. Quantitatively transfer the contents of the tube to a 250-milliliter volumetric flask. Add approximately 200 milliliters of freshly boiled and cooled distilled water, then 4.0 milliliters of 7.5 *N* $NH_4OH$, and dilute to volume with freshly boiled and cooled distilled water. Treat a sample of the oxacillin working standard in the same manner. Determine the absorbance of the sample and working standard solutions on a suitable spectrophotometer at 235 nanometers against a reagent blank, and calculate as follows:

$$\text{Percent oxacillin} = \frac{\text{Absorbance of sample} \times \text{Weight in milligrams of standard} \times \text{oxacillin content of standard in percent}}{\text{Absorbance of standard} \times \text{Weight in milligrams of sample}}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* Use the sample solution prepared as described in paragraph (b)(5) of this section and record the ultraviolet spectrum between 230 nanometers and 260 nanometers. It should be basically identical to that of the standard similarly treated.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59858, Nov. 22, 1977; 49 FR 5096, Feb. 10, 1984; 50 FR 19918, 19919, May 13, 1985]

### § 440.49a Sterile oxacillin sodium monohydrate.

(a) *Requirements for certification—* (1) *Standards of identity, strength, quality, and purity.* Sterile oxacillin sodium monohydrate is the monohydrated sodium salt of 5-methyl-3-phenyl-4-isoxazolyl penicillin. It is so purified and dried that:

(i) It contains not less than 815 and not more than 950 micrograms of oxacillin per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 3.5 and not more than 5.0 percent.

(vi) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 4.5 and not more than 7.5.

(vii) Its oxacillin content is not less than 81.5 percent and not more than 95.0 percent.

(viii) It is crystalline.

(ix) It gives a positive identity test for the oxacillin moiety.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, oxacillin content, crystallinity, and identity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams, plus one package containing approximately 2 grams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5.0 micrograms of oxacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 20 milligrams of oxacillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using a solution containing 30 milligrams per milliliter.

(7) *Oxacillin content.* Proceed as directed in § 440.49(b)(5).

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Identity.* Proceed as directed in § 440.49(b)(7).

[39 FR 18976, May 30, 1974, as amended at 42 FR 59858, Nov. 22, 1977; 50 FR 19918, 19919, May 13, 1985]

### § 440.55a Sterile penicillin G benzathine.

(a) *Requirements for certification—* (1) *Standards of identity, strength, quality, and purity.* Penicillin G benzathine is the *N,N′*- dibenzylethylenediamine salt of penicillin G. It is so purified and dried that:

(i) Its potency is not less than 1,090 units and not more than 1,272 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 5.0 percent and not more than 8 percent.

(vi) Its pH in a 1:1 mixture of absolute ethyl alcohol and water containing 0.5 milligram per milliliter is not less than 4.0 and not more than 6.5.

(vii) Its penicillin G content is not less than 57.9 percent and not more than 71.6 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately measured representative portion of the sample in sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately, further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, medium F in lieu of medium E, and during the period of incubation shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in § 436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, except prepare the sample as follows: Dissolve 50 milligrams of sample with 50 milliliters of absolute ethyl alcohol. Add 50 milliliters of distilled water and mix well.

(7) *Penicillin G content.* Accurately weigh approximately 50 milligrams of the sample, dissolve in absolute methyl alcohol, and dilute to 100 milliliters with absolute methyl alcohol. Treat a portion of the working standard in the same manner. Using a suitable spectrophotometer equipped with a quartz cell and absolute methyl alcohol as the blank, determine the absorbance at 263 nanometers. Calculate the percent penicillin G as follows:

$$\text{Percent penicillin G} = \frac{\text{Absorbance of sample} \times \text{weight in milligrams of standard} \times \text{percent penicillin G in standard}}{\text{Absorbance of standard} \times \text{weight in milligrams of sample}}$$

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[42 FR 59858, Nov. 22, 1977, as amended at 45 FR 16472, Mar. 14, 1980; 49 FR 6092, Feb. 17, 1984; 50 FR 19918, 19919, May 13, 1985]

### § 440.71 Penicillin V.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V is 3,3-dimethyl - 7-oxo-6-(2-phenoxyacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 1,525 units nor more than 1,780 units per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 2.0 percent.

(iv) Its pH in a saturated aqueous solution is not less than 2.5 and not more than 4.0.

(v) Its penicillin V content is not less than 90 percent and not more than 105 percent.

(vi) It is crystalline.

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the statement ''For use in the manufacture of nonparenteral drugs only.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, penicillin V content, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*— (1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the bioassay method shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample (approximately 30 milligrams) in 2.0 milliliters of absolute methyl alcohol. Further dilute an aliquot of this solution with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a saturated aqueous solution prepared by adding approximately 30 milligrams per milliliter.

(5) *Penicillin V content.* Accurately weigh approximately 20 milligrams of the sample, dissolve in absolute methanol, and make to 100 milliliters with absolute methyl alcohol. Treat a portion of the working standard in the same manner. Using a suitable spectrophotometer equipped with a quartz cell and absolute methyl alcohol as the blank, determine the absorbance of the peak at 276 nanometers. Calculate the percent penicillin V as follows:

$$\text{Percent penicillin V} = \frac{\text{Absorbance of sample} \times \text{weight in milligrams of standard} \times \text{Percent penicillin V in standard}}{\text{Absorbance of standard} \times \text{Weight in milligrams of sample}}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[42 FR 59859, Nov. 22, 1977, as amended at 50 FR 19918, 19919, May 13, 1985]

### § 440.73 Penicillin V potassium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium is the potassium salt of 3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido) - 4 -thia - 1

- azabicyclo[3.2.0]heptane - 2 - carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 1,380 units nor more than 1,610 units per milligram.

(ii) [Reserved]

(iii) Its loss on drying is not more than 1.5 percent.

(iv) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 4.0 and not more than 7.5.

(v) Its penicillin V content is not less than 81.2 percent and not more than 94.7 percent.

(vi) It is crystalline.

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the statement ''For use in the manufacture of nonparental drugs only.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, loss on drying, pH, penicillin V content, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 30 milligrams per milliliter.

(5) *Penicillin V content.* Dissolve and dilute approximately 20 milligrams of the sample, accurately weighed to 100 milliliters with 0.1*N* sodium hydroxide solution. Treat a portion of the penicillin V working standard in the same manner. Using a suitable spectrophotometer equipped with a quartz cell and 0.1*N* sodium hydroxide solution as the blank, determine the absorbance of the peak at 275 nanometers. Calculate the percent penicillin V as follows:

$$\text{Percent penicillin V} = \frac{\text{Absorbance of sample} \times \text{Weight in milligrams of standard} \times \text{Percent penicillin V in standard}}{\text{Absorbance of standard} \times \text{Weight in milligrams of sample}}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[42 FR 59859, Nov. 22, 1977, as amended at 50 FR 19918, 19919, May 13, 1985]

### § 440.74a Sterile penicillin G procaine.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G procaine is 3,3 - dimethyl - 7 - oxo - 6 - (2 - phenylacetamido) - 4 - thia - 1 - azabicyclo [3.2.0]heptane-2-carboxylic acid 2-(diethylamino) ethyl *p*-aminobenzoate compound (1:1). It is so purified and dried that:

(i) Its potency is not less than 900 units and not more than 1,050 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 2.8 percent and not more than 4.2 percent.

(vi) Its pH in a saturated aqueous solution (about 300 milligrams per milliliter) is not less than 5.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 51.0 percent and not more than 59.6 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed § 436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except add sufficient penicillinase to diluting fluid A and swirl the flask to completely solubilize the sample before filtration. If the product contains lecithin, use diluting fluid D in lieu of A.

(3) *Pyrogens.* Proceed as directed in § 436.32(h) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using a saturated solution prepared by suspending 300 milligrams of sample per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[42 FR 59860, Nov. 22, 1977, as amended at 45 FR 16472, Mar. 14, 1980; 45 FR 22921, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### § 440.80 Penicillin G potassium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality and purity.* Penicillin G potassium is potassium 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 1,440 units and not more than 1,680 units per milligram.

(ii) Its loss on drying is not more than 1.5 percent.

(iii) The pH of an aqueous solution containing 60 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(iv) Its penicillin G content is not less than 80.8 percent and not more than 94.3 percent.

(v) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of test and assays on the batch for potency, loss on drying, pH, penicillin G content, and crystrallinity.

(ii) Samples, if required by the Center for Drug Evaluation and Research: 10 packages, each containing approximately 300 milligrams.

(b) *Test and methods of assay*—(1) *Potency*. Proceed as directed in § 440.80a(b)(1).

(2) *Loss on drying*. Proceed as directed in § 436.200(b) of this chapter.

(3) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(4) *Penicillin G content*. Proceed as directed in § 436.316 of this chapter.

(5) *Crystallinity*. Proceed as directed in § 436.203(a) of this chapter.

[55 FR 38674, Sept. 20, 1990]

### § 440.80a Sterile penicillin G potassium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Penicillin G potassium is potassium 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 1,440 units and not more than 1,680 units per milligram. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH in an aqueous solution containing 60 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 80.8 percent and not more than 94.3 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay*. Proceed as directed in § 436.205 of this chapter.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

(6) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in §436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

[42 FR 59860, Nov. 22, 1977, as amended at 45 FR 16472, Mar. 14, 1980; 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### §440.81a Sterile penicillin G sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G sodium is sodium 3,3-dimethyl-7-oxo-6-(2 - phenylacetamido) - 4 - thia - 1 - azabicyclo [3.2.0] heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 1,500 units and not more than 1,750 units per milligram. If it is packaged for dispensing, its content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH in an aqueous solution containing 60 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 84.5 percent and not more than 98.5 percent.

(viii) It is crystalline.

(ix) It passes the test for heat stability if it does not show a loss of more than 10 percent of its original potency.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, penicillin G content, crystallinity, and heat stability.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative aliquot from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Heat stability.* Proceed as directed in § 436.214 of this chapter.

[42 FR 59861, Nov. 22, 1977, as amended at 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### § 440.83a Sterile piperacillin sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile piperacillin sodium is the sodium salt of (2*S*,5*R*, 6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 863 micrograms and not more than 1,007 micrograms of piperacillin per milligram on an anhydrous basis. If it is packaged for dispensing, it contains not less than 90.0 percent and not more than 120.0 percent of the number of grams of piperacillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 1.0 percent.

(vi) Its pH in an aqueous solution containing 400 milligrams per milliliter is not less than 5.5 and not more than 7.5.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.334 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 150 milligrams of piperacillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the sample preparation method described in paragraph (d)(4) of that section.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 400 milligrams per milliliter

[47 FR 15769, Apr. 13, 1982, as amended at 50 FR 19918, 19919, May 13, 1985]

### § 440.90a Sterile ticarcillin disodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile ticarcillin disodium is 6-[(carboxy-3-thienylacetyl)] amino - 3, 3-dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptane-2-carboxylic acid disodium salt. It is so purified and dried that:

(i) It contains not less than 800 micrograms of ticarcillin per milligram on an anhydrous basis. If it is packaged for dispensing, its ticarcillin content is not less than 90 percent and

not more than 115 percent of the number of milligrams of ticarcillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 6.0 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams of ticarcillin per milliliter (or if packaged for dispensing after reconstitution as directed in the labeling) is not less than 6.0 and not more than 8.0.

(vii) It gives a positive identity test for ticarcillin.

(viii) Its ticarcillin content is not less than 80 percent and not more than 94 percent on an anhydrous basis.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, identity, and ticarcillin content.

(ii) Samples required:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; and also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. If it is a single-dose container, use a separate needle and syringe for each container. Dilute with sufficient solution 1 to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5.0 micrograms of ticarcillin per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 100 milligrams of ticarcillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams of ticarcillin per milliliter (or if packaged for dispensing, use a solution prepared as directed for reconstitution in the labeling).

(7) *Identity and ticarcillin content.* Transfer an accurately weighed portion of approximately 40 milligrams of the sample to a 100-milliliter volumetric flask. Dissolve and dilute to volume with distilled water. Transfer 5.0 milliliters of this solution to another 100-milliliter volumetric flask and dilute to volume with 0.1*N* methanolic hydrochloric acid (prepared by diluting 0.8 milliliter of 12*N* hydrochloric acid to 100 milliliters with methyl alcohol). Treat a portion of the ticarcillin standard in the same manner. Using a suitable spectrophotometer equipped with a 1.0-centimeter quartz cell and 0.1*N* methanolic acid as a blank, scan the absorption spectrum of the methanolic solution of the sample and the standard between the wavelengths of 300 and 200 nanometers. Determine the absorbance of each solution at the maxima, at approximately 230 nanometers. The spectrum of the samples should compare qualitatively with

that of the ticarcillin working standard. Determine the percent ticarcillin as follows:

$$\text{Percent ticarcillin} = \frac{\text{Absorbance of sample} \times \text{Weight in milligrams of standard} \times \text{Potency of standard in micrograms per milligram} \times 10}{\text{Absorbance of standard} \times \text{weight in milligrams of sample} \times (100 - m)}$$

where: $m$=Percent moisture in the sample.

[42 FR 14093, Mar. 15, 1977, as amended at 50 FR 19918, 19919, May 13, 1985]

### § 440.91 Ticarcillin monosodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ticarcillin monosodium monohydrate is 6-[(carboxy-3-thienylacetyl)] amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid monosodium salt monohydrate. It is so purified and dried that:

(i) Its ticarcillin potency is not less than 890 micrograms of ticarcillin per milligram calculated on an anhydrous basis.

(ii) Its moisture content is not less than 4.0 and not more than 6.0 percent.

(iii) The pH of an aqueous solution containing 10 milligrams of ticarcillin per milliliter is not less than 2.5 and not more than 4.0.

(iv) It gives a positive identity test for ticarcillin.

(v) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Center for Drug Evaluation and Research: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Ticarcillin potency.* Determine the micrograms of ticarcillin activity per milligram of sample. Proceed as directed in § 436.355 of this chapter using the equipment, conditions, reagents, and system suitability requirements as described in § 440.290b(b), except use the resolution test solution to determine resolution in lieu of the working standard solution. Prepare the working standard solution, sample solution, and resolution test solution and calculate the micrograms of ticarcillin per milligrams as follows:

(i) *Preparation of working standard, sample, and resolution test solutions*—(A) *Working standard solution.* Accurately weigh a quantity of the ticarcillin working standard containing the equivalent of approximately 90 milligrams of ticarcillin activity and transfer to a 100-milliliter volumetric flask. Dissolve and dilute to volume with diluent pH 6.4 phosphate buffer prepared as described in § 440.290b(b)(1)(i)(*c*).

(B) *Sample solution.* Dissolve an accurately weighed portion of the sample with diluent pH 6.4 buffer as prepared in § 440.290b(b)(1)(i)(*c*) to obtain a solution containing 0.9 milligram of ticarcillin activity per milliliter (estimated).

(C) *Resolution test solution.* Accurately weigh a quantity of the ticarcillin working standard containing the equivalent of approximately 90 milligrams of ticarcillin activity and transfer to a 100-milliliter volumetric flask. Prepare a solution of the clavulanic acid working standard containing the equivalent of 30 milligrams of clavulanic acid activity in a 100-milliliter volumetric flask. Dissolve and dilute to volume with diluent. Transfer 10 milliliters of this solution into the flask containing the ticarcillin standard. Dilute the combined standard solution to volume with diluent and mix. Use within 8 hours of preparation.

(ii) *Calculations.* Calculate the micrograms of ticarcillin per milligram as follows:

$$\text{Milligrams of amoxicillin or clavulanic acid per milliliter} = \frac{A_u \times C \times V \times 0.5}{A_s}$$

where:

$A_u$=Area of the ticarcillin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ticarcillin peak in the chromatogram of the ticarcillin working standard;

$P_s$=Ticarcillin activity in the ticarcillin working standard solution in micrograms per milliliter;

$C_u$=Milligrams of ticarcillin sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams of ticarcillin per milliliter.

(4) *Identity.* Proceed as directed in §440.90a(b)(7).

(5) *Crystallinity.* Proceed as directed in §436.203 of this chapter.

[55 FR 5839, Feb. 20, 1990]

## Subpart B—Oral Dosage Forms

### §440.103 Amoxicillin oral dosage forms.

### §440.103a Amoxicillin trihydrate capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate capsules are composed of amoxicillin trihydrate with or without one or more suitable and harmless lubricants, diluents, and drying agents, enclosed in a gelatin capsule. Each capsule contains amoxicillin trihydrate equivalent to 250 milligrams or 500 milligrams of amoxicillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its moisture content is not more than 14.5 percent. It passes the identity test. The amoxicillin trihydrate used conforms to the standards prescribed by §440.3(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''amoxicillin capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, and identity.

(ii) Samples required:

(*a*) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive:

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of amoxicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Place the contents of a representative number of capsules into a high-speed glass blender jar and add sufficient distilled water to give a convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot with distilled water to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Identity.* Proceed as directed in § 436.311 of this chapter, preparing the sample solution as follows: Dissolve an accurately weighed portion of the amoxicillin capsule contents in 0.1*N* hydrochloric acid to give a solution containing 4 milligrams of amoxicillin per milliliter.

[39 FR 34033, Sept. 23, 1974, as amended at 49 FR 3458, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.103b Amoxicillin trihydrate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate for oral suspension is a mixture of amoxicillin trihydrate with one or more suitable and harmless colorings, flavorings, buffers, sweetening ingredients, preservatives, stabilizers, and suspending agents. When reconstituted as directed in the labeling, it contains amoxicillin trihydrate equivalent to either 25 or 50 milligrams of amoxicillin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its moisture content is not more than 3.0 percent. Its pH, when reconstituted as directed in the labeling, is not less than 5.0 and not more than 7.5. It passes the identity test. The amoxicillin trihydrate used conforms to the standards prescribed by § 440.3(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled ''amoxicillin for oral suspension''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, pH, and identity.

(ii) Samples required:

(*a*) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive:

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured representative portion of the sample into a suitable volumetric flask and dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Mix well. Further dilute an aliquot with solution 3 to the reference concentration of 0.1 microgram of amoxicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured aliquot (usually a single dose) into an appropriately sized volumetric flask and dilute to volume with distilled water. Mix well. Further dilute with distilled water to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension reconstituted as directed in the labeling.

(4) *Identity.* Proceed as directed in § 436.311 of this chapter, preparing the sample solution as follows: From an aliquot of suspension prepared in accordance with the label, make either a 6.25:1 dilution for the 25-milligrams-per-milliliter dosage; or a 12.5:1 dilution for the 50-milligrams-per-milliliter dosage, with 0.1*N* hydrochloric acid. The slight dilution of the acid

does not have a significant effect on the test.

[39 FR 34033, Sept. 23, 1974, as amended at 49 FR 3458, Jan. 27, 1984; 50 FR 19919, May 13, 1985; 54 FR 47351, Nov. 14, 1989]

### § 440.103c Amoxicillin trihydrate chewable tablets.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate chewable tablets are composed of amoxicillin trihydrate with or without one or more suitable lubricants, diluents, preservatives, drying agents, flavorings, and colorings. Each tablet contains amoxicillin trihydrate equivalent to either 125 or 250 milligrams of amoxicillin. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its moisture content is not more than 6.0 percent. It passes the identity test. The amoxicillin trihydrate used conforms to the standards prescribed by § 440.3(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by

§ 432.5 of this chapter, this drug shall be labeled ''amoxicillin tablets.''

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assay on:

(*a*) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, and identity.

(ii) Samples required:

(*a*) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and dilute with solution 3 to the reference concentration of 0.1 microgram of amoxicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 5 minutes. Further dilute with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Identity.* Proceed as directed in § 436.311 of this chapter, preparing the sample as follows: Using a mortar and pestle, grind a representative number of tablets into a fine powder. Dissolve an accurately weighed amount of this powder in 0.1*N* hydrochloric acid to give a solution containing 4 milligrams of amoxicillin per milliliter.

[45 FR 64569, Sept. 30, 1980, as amended at 50 FR 19919, May 13, 1985]

### § 440.103d Amoxicillin trihydrate and clavulanate potassium tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate and clavulanate potassium tablets are composed of amoxicillin trihydrate and clavulanate potassium with or without one or more suitable lubricants, diluents, and binders. Each tablet contains amoxicillin trihydrate equivalent to either 250 or 500 milligrams of amoxicillin and clavulanate potassium equivalent to 125 milligrams of clavulanic acid. Its amoxicillin trihydrate content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of clavulanic acid that it is represented to

contain. Its moisture content is not more than 7 percent if it contains 250 milligrams of amoxicillin and not more than 10 percent if it contains 500 milligrams of amoxicillin. It passes the dissolution test if the quantity *Q*, at 30 minutes, is 85 percent or greater if it contains 250 milligrams of amoxicillin and 75 percent or greater if it contains 500 milligrams of amoxicillin. The amoxicillin trihydrate conforms to the standards prescribed by §440.3(a)(1). The clavulanate potassium conforms to the standards prescribed by §455.15(a)(1) of this chapter.

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled *''amoxicillin and clavulanate potassium tablets''*.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(*b*) The clavulanate potassium used in making the batch for clavulanic acid content, moisture, pH, identity, and clavam-2-carboxylate content.

(*c*) The batch for amoxicillin content, clavulanic acid content, moisture, and dissolution rate.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of 100 tablets.

(b) *Tests and methods of assay*—(1) *Amoxicillin and clavulanic acid contents.* Proceed as directed in §436.351 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength between 220 and 230 nanometers, and a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded silica. Reagents, working standard and sample solutions, system suitability requirements, and calculations for amoxicillin or clavulanic acid content are as follows:

(i) *Reagents*—(*a*) *0.5M Sodium phosphate buffer solution, pH 4.4.* Transfer 7.8 grams of monobasic sodium phosphate to a 1-liter volumetric flask and dissolve in 900 milliliters of distilled water. Adjust the pH to 4.4 ± 0.1 with 18*N* phosphoric acid or 10*N* sodium hydroxide. Dilute to volume with distilled water. Mix well.

(*b*) *Mobile phase.* Mix methanol: 0.05*M* sodium phosphate buffer solution, pH 4.4 (5:95 v/v) and ultrasonicate for no less than 2 minutes. Degas by passing through a 0.5-micron filter with vacuum. The mobile phase may be sparged with the helium through a 2-micrometer metal filter for the duration of the analysis. Adjust the ratio of methanol to aqueous buffer as necessary to obtain satisfactory retention of the peaks.

(ii) *Working standard and sample solutions*—(*a*) *Preparation of working standard solution.* Accurately weigh and transfer into a 200-milliliter volumetric flask approximately 100 milligrams of amoxicillin working standard and approximately 50 milligrams of the clavulanic acid working standard. Dissolve and dilute to volume with distilled water. Use within 8 hours after preparation.

(*b*) *Preparation of sample solution.* To obtain a concentration of 0.5 milligram of amoxicillin per milliliter, dissolve a representative number of tablets in water with the aid of a magnetic stirrer or ultrasonication. Filter a small aliquot through Whatman #42 filter paper or equivalent, discarding the first 10 milliliters of filtrate. Alternatively, a suitable membrane filter may be used. Prepare samples not more than 1 hour before the chromatographic injection.

(iii) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5.

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 550 theoretical plates.

(*c*) *Resolution factor.* The resolution factor (*R*) between the clavulanic acid and amoxicillin peaks is satisfactory if it is not less than 3.5.

(*d*) *Coefficient of variation.* The coefficient of variation ($S_R$ in percent) is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in §436.351(b) of this chapter.

(iv) *Calculations.* Calculate the milligrams of amoxicillin or clavulanic acid content per tablet as follows:

$$\text{Milligrams of amoxicillin or clavulanic acid per tablet} = \frac{A_u \times C_s \times V}{A_s \times N}$$

where:

$A_u$=Response of the amoxicillin or clavulanic acid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Response of the amoxicillin or clavulanic acid peak in the chromatogram of the amoxicillin or clavulanic acid working standard;

$C_s$=Concentration of standards in milligrams of amoxicillin or clavulanic acid per milliliter of the standard solution;

$V$=Volume of sample solution (milliliters); and

N=Number of tablets taken for assay.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *Dissolution.* Proceed as directed in §436.215 of this chapter. Dissolution rate is determined by dissolution of the amoxicillin component using the high-performance liquid chromatographic assay described in this section.

[49 FR 39672, Oct. 10, 1984, as amended at 50 FR 19919, May 13, 1985; 55 FR 11582, Mar. 29, 1990]

### §440.103e Amoxicillin trihydrate and clavulanate potassium for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate and clavulanate potassium for oral suspension is a dry mixture of amoxicillin trihydrate and clavulanate potassium with one or more suitable and harmless colorings, flavorings, buffers, sweetening ingredients, preservatives, stabilizers, and suspending agents. When reconstituted as directed in the labeling, each milliliter contains either amoxicillin trihydrate equivalent to 25 milligrams of amoxicillin with clavulanate potassium equivalent to 6.25 clavulanic acid or amoxicillin trihydrate equivalent to 50 milligrams of amoxicillin with clavulanate potassium equivalent to 12.5 milligrams of clavulanic acid. Its amoxicillin trihydrate content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of clavulanic acid that it is represented to contain. The moisture content of the dry powder is not more than 7.5 percent when the reconstituted solution is to contain 25 milligrams of amoxicillin per milliliter and not more than 8.5 percent when the reconstituted solution is to contain 50 milligrams of amoxicillin per milliliter. When reconstituted as directed in the labeling, its pH is not less than 4.8 and not more than 6.6. The amoxicillin trihydrate used conforms to the standards prescribed by §440.3(a)(1). The clavulanate potassium conforms to the standards prescribed by §455.15(a)(1) of this chapter.

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''*amoxicillin and clavulanate potassium for oral suspension*''.

(3) *Requests for certification; samples.* In addition to the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(*b*) The clavulanate potassium used in making the batch for clavulanic acid content, moisture, pH, identity, and clavam-2-carboxylate content.

(*c*) The batch for amoxicillin content, clavulanic acid content, moisture, and pH.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Amoxicillin content or clavulanic acid content.* Proceed as directed in § 436.351 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength between 220 and 230 nanometers, and a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded silica. Reagents, working standard and sample solutions, system suitability requirments, and calculations for amoxicillin and clavulanic acid content are as follows:

(i) *Reagents*—(*a*) *0.05M Sodium phosphate buffer solution, pH 4.4.* Transfer 7.8 grams of monobasic sodium phosphate to a 1-liter volumetric flask and dissolve in 900 milliliters of distilled water. Adjust to pH 4.4 ± 0.1 with 18*N* phosphoric acid or 10*N* sodium hydroxide. Dilute to volume with distilled water. Mix well.

(*b*) *Mobile phase.* Mix methanol:0.05*M* sodium phosphate buffer solution, pH 4.4 (5:95 v/v) and mix or ultrasonicate for no less than 2 minutes. Degas by passing through a 0.5-micron filter with vacuum. The mobile phase may be sparged with helium through a 2-micrometer metal filter for the duration of the analysis. Adjust the ratio of methanol to aqueous buffer as necessary to obtain satisfactory retention of the peaks.

(ii) *Working standard and sample solutions*—(*a*) *Preparation of working standard solution.* Accurately weigh and transfer into a 200-milliliter volumetric flask approximately 100 milligrams of amoxicillin working standard and approximately 50 milligrams of the clavulanate working standard. Dissolve and dilute to volume with distilled water. Use within 8 hours after preparation.

(*b*) *Preparation of sample solution.* Reconstitute the suspension as directed in the labeling. Immediately transfer an appropriate aliquot to a suitable volumetric flask to obtain an approximate amoxicillin concentration of 0.5 milligram per milliliter and dilute to volume with distilled water. Mix well for 10 minutes using a magnetic stirrer. Filter an aliquot through Whatman #42 or equivalent filter paper. Alternatively, a suitable membrane filter may be used. Samples should be prepared just prior to chromatographic injection. Inject the sample solution within 1 hour after the addition of water.

(iii) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5.

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 550 theoretical plates.

(*c*) *Resolution factor.* The resolution factor (*R*) between the clavulanic acid and amoxicillin peaks is satisfactory if it is not less than 3.5.

(*d*) *Coefficient of variation.* The coefficient of variation ($S_R$ in percent) is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in § 436.351(b) of this chapter.

(iv) *Calculations.* Calculate the quantity of amoxicillin or clavulanic acid content in milligrams per milliliter of the oral suspension as follows:

$$\text{Milligrams of amoxicillin or clavulanic acid per milliliter} = \frac{A_u \times C \times V \times 0.5}{A_s}$$

Where:

$A_u$=Response of the amoxicillin or clavulanic acid peaks in the sample chromatogram;

$A_s$=Response of the amoxicillin or clavulanic acid peaks in the standard chromatogram;

*C*=Concentration of the standard (milligrams per milliliter of amoxicillin X potency of amoxicillin standard or milligrams per milliliter of clavulanate X potency of clavulanate standard); and

V=Dilution volume in milliliters.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension

reconstituted as directed in the labeling.

[49 FR 39673, Oct. 10, 1984, as amended at 50 FR 19919, May 13, 1985; 55 FR 11582, Mar. 29, 1990]

### § 440.103f Amoxicillin trihydrate-clavulanate potassium chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate-clavulanate potassium chewable tablets are composed of amoxicillin trihydrate and clavulanate potassium with or without one or more suitable lubricants, diluents, flavorings, and binders. Each tablet contains amoxicillin trihydrate equivalent to either 125 or 250 milligrams of amoxicillin and clavulanate potassium equivalent to 31.25 or 62.5 milligrams of clavulanic acid. Its amoxicillin trihydrate content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of clavulanic acid that it is represented to contain. Its moisture content is not more than 6 percent. It passes the dissolution test if the quantity *Q,* of amoxicillin at 30 minutes, is 85 percent or greater. The amoxicillin trihydrate conforms to the standards prescribed by § 440.3(a)(1). The clavulanate potassium conforms to the standards prescribed by § 455.15(a)(1) of this chapter.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled ''*amoxicillin-clavulanate potassium chewable tablets*''.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The amoxicillin trihydrate used in making the batch for potency, safety, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(*b*) The clavulanate potassium used in making the batch for clavulanic acid content, moisture, pH, identity, and clavam-2-carboxylate content.

(*c*) The batch for amoxicillin content, clavulanic acid content, moisture, and dissolution rate.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of 100 tablets.

(b) *Tests and methods of assay*—(1) *Amoxicillin and clavulanic acid contents.* Proceed as directed in § 436.351 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength between 220 and 230 nanometers, and a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas. Reagents, working standard and sample solutions, system suitability requirements, and calculations for amoxicillin or clavulanic acid content are as follows:

(i) *Reagents*—(*a*) *0.05M Sodium phosphate buffer solution, pH 4.4.* Transfer 7.8 grams of sodium monobasic phosphate to a 1-liter volumetric flask and dissolve in 900 milliliters of distilled water. Adjust the pH to 4.4±0.1 with 18*N* phosphoric acid or 10*N* sodium hydroxide. Dilute to volume with distilled water. Mix well.

(*b*) *Mobile phase.* Mix methanol: 0.05*M* sodium phosphate buffer solution, pH 4.4 (5:95 v/v) and ultrasonicate for no less than 2 minutes. Degas by passing through a 0.5-micron filter with vacuum. The mobile phase may be sparged with the helium through a 2-micrometer metal filter for the duration of the analysis. Adjust the ratio of methanol to aqueous buffer as necessary to obtain satisfactory retention of the peaks.

(ii) *Working standard and sample solutions—(a) Preparation of working standard solution.* Dissolve and dilute accurately weighed portions each of the

amoxicillin trihydrate working standard and the clavulanate lithium working standard with water to obtain a solution containing 0.5 milligram of amoxicillin and 0.25 milligram of clavulanic acid per milliliter. Use within 1 hour after preparation or within 4 hours if stored under refrigeration.

(*b*) *Preparation of sample solution.* To obtain a concentration of 0.5 milligram of amoxicillin per milliliter, dissolve a representative number of tablets in water with the aid of a magnetic stirrer or ultrasonication. Filter an aliquot through Whatman #42 filter paper or equivalent, discard the first 10 milliliters of filtrate, and use the remaining portion as the sample solution. Alternatively, a suitable membrane filter may be used. Prepare samples not more than 1 hour before the chromatographic injection.

(iii) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5.

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,000 theoretical plates in a 30-centimeter column for each active component.

(*c*) *Resolution.* The resolution (*R*) between the clavulanic acid and amoxicillin peaks is satisfactory if it is not less than 3.5.

(*d*) *Coefficient of variation.* The coefficient of variation ($S_R$ in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in § 436.351(b) of this chapter.

(iv) *Calculations.* Calculate the milligrams of amoxicillin or clavulanic acid content per tablet as follows:

$$\text{Milligrams of amoxicillin or clavulanic acid per tablet} = \frac{A_u \times C_s \times V}{A_s \times N}$$

where

$A_u$=Response of the amoxicillin or clavulanic acid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Response of the amoxicillin or clavulanic acid peak in the chromatogram of the amoxicillin or clavulanic acid working standard;

$C_s$=Concentration of standards in milligrams of amoxicillin or clavulanic acid per milliliter of the standard solution;

$V$=Volume of sample solution (milliliters); and

N=Number of tablets taken for assay.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Dissolution.* Proceed as directed in § 436.215 of this chapter. Dissolution rate is determined by dissolution of the amoxicillin component using the high-performance liquid chromatographic assay described in this section.

[50 FR 42933, Oct. 25, 1985; 50 FR 47367, Nov. 17, 1985, as amended at 55 FR 11582, Mar. 29, 1990]

## § 440.105 Ampicillin oral dosage forms.

### § 440.105a Ampicillin tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin tablets are composed of ampicillin with one or more suitable and harmless diluents and lubricants. Each tablet contains 250 or 500 milligrams of ampicillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its loss on drying is not more than 4 percent. The tablets disintegrate within 15 minutes. The ampicillin used conforms to the standards prescribed by § 440.5(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, loss on drying, and disintegration time.

(ii) Samples required:

(*a*) The ampicillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Place a representative number of tablets in a high-speed glass blender jar and add sufficient distilled water to give a convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot with distilled water to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in §436.200(a) of this chapter.

(3) *Disintegration time.* Proceed as directed in §436.212 of this chapter, using the procedure described in paragraph (e)(1) of that section.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3458, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### §440.105b Ampicillin chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Each ampicillin chewable tablet contains 125 milligrams or 250 milligrams of ampicillin with suitable binders, lubricants, flavorings, and colorings. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its loss on drying is not more than 3 percent. The ampicillin used conforms to the standards prescribed by §440.5(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''ampicillin tablets''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) The results of tests and assays on:

(*a*) The ampicillin used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The ampicillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Blend a representative number of tablets in a high-speed blender with sufficient distilled water to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with distilled water to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in §436.200(a) of this chapter.

[39 FR 18976, May 30, 1974, as amended at 43 FR 9800, Mar. 10, 1978; 49 FR 3458, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.105c Ampicillin capsules.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Ampicillin capsules are composed of ampicillin with or without one or more buffer substances, diluents, binders, lubricants, vegetable oils, colorings, and flavorings, enclosed in a gelatin capsule. Each capsule contains 125 milligrams, 250 milligrams, or 500 milligrams of ampicillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. The loss on drying is not more than 4.0 percent. The ampicillin used conforms to the standards prescribed by § 440.5(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The ampicillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Place the contents of a representative number of capsules into a high-speed glass blender jar and add sufficient distilled water to give a convenient concentration. Blend for 3 to 5 minutes. Filter through Whatman No. 2 filter paper. Further dilute an aliquot of the filtrate with distilled water to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3458, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.105d Ampicillin for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin for oral suspension is a mixture of ampicillin with one or more suitable and harmless colorings, flavorings, buffer substances, sweetening ingredients, and preservatives. When reconstituted as directed in the labeling, it contains either 25 milligrams, 50 milligrams, or 100 milligrams of ampicillin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its moisture content is not more than 2.5 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The ampicillin used conforms to the standards prescribed by § 440.5(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The ampicillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*. Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured representative portion of the sample into a suitable volumetric flask and dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a convenient concentration. Mix well. Further dilute an aliquot with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured aliquot (usually a single dose) into an appropriately sized volumetric flask and dilute to volume with distilled water. Mix well. Further dilute with distilled water to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3458, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### §440.107 Ampicillin trihydrate oral dosage forms.

### §440.107a Ampicillin trihydrate chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate chewable tablets are composed of ampicillin trihydrate with or without one or more suitable diluents, lubricants, preservatives, and flavorings. Each tablet contains ampicillin trihydrate equivalent to 125 or 250 milligrams of ampicillin. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its moisture content is not more than 5.0 percent. The ampicillin trihydrate used conforms to the standards prescribed by §440.7(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''ampicillin tablets.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard

solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient distilled water to give a convenient concentration. Blend for 5 minutes. Further dilute with distilled water to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3459, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.107b Ampicillin trihydrate capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate capsules are composed of ampicillin trihydrate with or without one or more buffer substances, diluents, binders, lubricants, vegetable oils, colorings, and flavorings enclosed in a gelatin capsule. Each capsule contains ampicillin trihydrate equivalent to 250 milligrams or 500 milligrams of ampicillin. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its loss on drying is not less than 10 percent and not more than 15 percent. The ampicillin trihydrate used conforms to the standards prescribed by § 440.7(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled ''ampicillin capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Place the contents of a representative number of capsules into a high-speed glass blender jar and add sufficient distilled water to give a convenient concentration. Blend for 3 to 5 minutes. Filter through Whatman No. 2 filter paper. Further dilute an aliquot of the filtrate with distilled water to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3459, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.107c Ampicillin trihydrate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate for oral suspension is a mixture of ampicillin trihydrate with one or more suitable and harmless colorings, flavorings, buffers, sweetening ingredients, and preservatives. When reconstituted as directed in the labeling, it contains ampicillin trihydrate equivalent to either 25, 50, or 100 milligrams of ampicillin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin

that it is represented to contain. Its moisture content is:

(i) Not more than 2.5 percent if it contains sugar and is intended to contain the equivalent of 25 or 50 milligrams of ampicillin per milliliter when reconstituted as directed in the labeling; or

(ii) Not more than 5 percent if it contains sugar and is intended to contain the equivalent of 100 milligrams of ampicillin per milliliter when reconstituted as directed in the labeling; or

Its pH, when reconstituted as directed in the labeling, is not less than 5.0 and is not more than 7.5. The ampicillin trihydrate used conforms to the standards prescribed by §440.7(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''ampicillin for oral suspension.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured representative portion of the sample into a suitable volumetric flask and dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a convenient concentration. Mix well. Further dilute an aliquot with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured aliquot (usually a single dose) into an appropriately sized volumetric flask and dilute to volume with distilled water. Mix well. Further dilute with distilled water to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3459, Jan. 27, 1984; 49 FR 5096, Feb. 10, 1984; 50 FR 19919, May 13, 1985]

### §440.107d Ampicillin trihydrate-probenecid for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate and probenecid for oral suspension is a dry mixture of ampicillin trihydrate and probenecid with suitable flavorings, lubricants, colorings, and suspending agents packaged in a single-dose container. When reconstituted as directed in the labeling, each single dose will contain ampicillin trihydrate equivalent to 3.5 grams of ampicillin and 1.0 gram of probenecid. Its ampicillin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of grams of ampicillin that it is represented to contain. Its probenecid content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of grams of probenecid that it is represented to contain. Its moisture content is not more than 5.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The ampicillin trihydrate used conforms to the standards prescribed by §440.7(a)(1). The probenecid used conforms to the standards prescribed by the U.S.P.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled ''ampicillin-probenecid for oral suspension''.

(3) *Requests for certification, samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The probenecid used in making the batch for all U.S.P. specifications.

(*c*) The batch for ampicillin content, probenecid content, moisture, and pH.

(ii) Samples required:

(*a*) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 10 immediate containers.

(b) *Tests and methods of assay*—(1) *Ampicillin content*—(i) *Sample preparation.* Reconstitute as directed in the labeling and mix well. Drain the suspension from the bottle for 30 seconds into a high-speed glass blender jar containing sufficient sterile distilled water to obtain a total volume of 500 milliliters. Blend for 10 minutes.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the aqueous solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Dilute an aliquot of the aqueous solution to the prescribed concentration.

(2) *Probenecid content*—(i) *Preparation of standard solution.* Transfer approximately 25 milligrams of U.S.P. probenecid reference standard, accurately weighed, to a 25-milliliter volumetric flask. Dissolve and dilute to volume with 1 percent aqueous sodium carbonate solution.

(ii) *Preparation of sample solution.* Reconstitute the sample as directed in the labeling and mix well. Drain the suspension from the bottle for 30 seconds into a 1,000-milliliter volumetric flask. Dilute to volume with 1 percent aqueous sodium carbonate solution, shake well, and filter through Whatman No. 6 filter paper. Discard the first 10-milliliter portion.

(iii) *Procedure.* Transfer 2.0 milliliters of the clear filtrate to a 125-milliliter separatory funnel and add 8.0 milliliters of 1.0*N* hydrochloric acid. Extract the solution with four 20-milliliter portions of chloroform, filtering each extract through a glass wool pledget into a 100-milliliter volumetric flask. Wash the pledget with chloroform, dilute to volume with chloroform and mix. Treat 2.0 milliliters of the standard solution in the same manner. Using a suitable spectrophotometer equipped with a 1-centimeter cell and chloroform washed with 1 percent aqueous sodium carbonate solution as a blank, determine the absorbance of the sample and standard solutions at the peak near 257 nanometers.

(iv) *Calculations.* Calculate the probenecid content as follows:

Grams probenecid per container=(Absorbance of sample×weight of standard in milligrams×percent purity of standard)/(Absorbance of standard×25×100)

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 40 FR 49083, Oct. 21, 1975; 49 FR 3459, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.107e Ampicillin trihydrate-probenecid capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate-probenecid capsules are composed of ampicillin trihydrate and probenecid with or without one or more buffer substances, diluents, binders, lubricants,

vegetable oils, colorings, and flavorings enclosed in a gelatin capsule. Each capsule contains ampicillin trihydrate equivalent to 389 milligrams of ampicillin and 111 milligrams of probenecid. Its ampicillin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its probenecid content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of probenecid that it is represented to contain. Its loss on drying is not less than 8.5 percent and not more than 13.0 percent. The ampicillin trihydrate used conforms to the standards prescribed by §440.7(a)(1). The probenecid used conforms to the standards prescribed by the U.S.P.

(2) *Labeling.* In addition to the labeling requirements prescribed by §432.5 of this chapter, this drug shall be labeled ''ampicillin-probenecid capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The probenecid used in making the batch for all U.S.P. specifications.

(*c*) The batch for ampicillin content, probenecid content, and loss on drying.

(ii) Samples required:

(*a*) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Ampicillin content.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 8 to 10 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Prepare the sample as follows: Place the contents of a representative number of capsules into a high-speed glass blender jar with sufficient distilled water to give a convenient concentration. Blend for 8 to 10 minutes. Filter through Whatman No. 2 filter paper. Further dilute an aliquot of the filtrate with distilled water to the prescribed concentration.

(2) *Probenecid content*—(i) *Preparation of standard solution.* Transfer approximately 25 milligrams of probenecid reference standard U.S.P., accurately weighed, to a 25-milliliter volumetric flask. Dissolve and dilute to volume with 1 percent aqueous sodium carbonate solution.

(ii) *Preparation of sample solution.* Place the contents of a representative number of capsules into a high-speed glass blender jar with 100 milliliters of 1 percent aqueous sodium carbonate solution for each capsule. Blend for 8 to 10 minutes. Filter a portion through Whatman No. 2 filter paper, discarding the first 10-milliliter portion of the filtrate.

(iii) *Procedure.* Transfer 2.0 milliliters of the clear filtrate to a 125-milliliter separatory funnel and add 8.0 milliliters of 1.0*N* hydrochloric acid. Extract the solution with four 20-milliliter portions of chloroform, filtering each extract into a 100-milliliter volumetric flask through a glass wool pledget and 6 grams of chloroform-washed anhydrous sodium sulfate. Wash the pledget and sodium sulfate with chloroform, dilute to volume with chloroform and mix. Treat 2.0 milliliters of the standard solution in the same manner. Using a suitable spectrophotometer equipped with a 1-centimeter cell and chloroform washed with 1 percent aqueous sodium carbonate solution as a blank, determine the absorbance of the sample

and standard solutions at the peak near 257 nanometers.

(iv) *Calculations.* Calculate the probenecid content as follows:

Milligrams probenecid per capsule = (Absorbance of sample × weight of standard in milligrams × percent purity of standard)/(Absorbance of standard × 25)

(3) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

[40 FR 58288, Dec. 16, 1975, as amended at 45 FR 16474, Mar. 14, 1980; 49 FR 3459, Jan. 27, 1984; 50 FR 19919, May 13, 1985]

### § 440.108 Bacampicillin hydrochloride dosage forms.

### § 440.108a Bacampicillin hydrochloride tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Bacampicillin hydrochloride tablets are composed of bacampicillin hydrochloride with one or more suitable and harmless diluents and lubricants. Each tablet contains bacampicillin hydrochloride equivalent to either 280 or 560 milligrams of ampicillin. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of ampicillin that it is represented to contain. Its moisture content is not more than 2.5 percent. It passes the dissolution test. The bacampicillin hydrochloride used conforms to the standards prescribed by § 440.8(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The bacampicillin hydrochloride used in making the batch for potency, moisture, pH, and identity.

(*b*) The batch for potency, moisture, and dissolution.

(ii) Samples required:

(*a*) The bacampicillin hydrochloride used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 100 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Hydroxylamine colorimetric assay.* Proceed as directed in § 440.8(b)(1)(i) of this chapter, except prepare the sample solution and calculate the potency of the sample as follows:

(*a*) *Preparation of sample solution.* Place one tablet into a high-speed glass blender jar with sufficient distilled water to obtain a concentration of 1.25 milligrams of ampicillin per milliliter (estimated). Blend for 3 to 5 minutes. Filter before using.

(*b*) *Calculations.* Calculate the ampicillin content in milligrams per tablet as follows:

$$\text{Milligrams of cyclacillin per tablet} = \frac{A_u \times P_a \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Absorbance of sample solution;

$P_a$=Potency of working standard in micrograms per milliliter;

$A_s$=Absorbance of working standard solution; d=Dilution factor of the sample.

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except use the ampicillin working standard. Prepare the sample as follows: Dissolve and dilute a representative number of tablets with distilled water to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Dissolution.* Proceed as directed in § 436.215 of this chapter, except in lieu of paragraph (d) of that section use the interpretation described in the United States Pharmacopeia XX dissolution test. The quantity, *Q* (the amount of ampicillin dissolved) is 85 percent at 30 minutes.

[46 FR 25604, May 8, 1981. Redesignated at 47 FR 23711, June 1, 1982, and amended at 48 FR 51293, 51294, Nov. 8, 1983; 50 FR 19919, May 13, 1985]

### § 440.108b Bacampicillin hydrochloride for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Bacampicillin hydrochloride for oral suspension is a mixture of bacampicillin hydrochloride

with one or more suitable and harmless buffers, diluents, sweetening ingredients, suspending agents, flavorings, and colorings. When reconstituted as directed in the labeling, it contains bacampicillin hydrochloride equivalent to 17.5 milligrams of ampicillin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of ampicillin that it is represented to contain. Its loss on drying is not more than 2.0 percent. When reconstituted as directed in the labeling, its pH is not less than 6.5 and not more than 8.0. It gives a positive identity test for bacampicillin hydrochloride. The bacampicillin hydrochloride conforms to the standards prescribed by § 440.8(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The bacampicillin used in making the batch for potency, moisture, pH, and identity.

(*b*) The batch for potency, loss on drying, pH, and identity.

(ii) Samples required:

(*a*) The bacampicillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.204 of this chapter, except:

(i) Use the ampicillin working standard as the standard of comparison;

(ii) Use 4.0 milliliters of sample solution in lieu of the 2.0 milliliters specified in paragraph (c)(1) of that section; and

(iii) Calculate the potency of the sample as follows:

$$\text{Milligrams of ampicillin per dose} = \frac{V_u \times F \times d}{n \times 4{,}000}$$

Prepare the sample as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured portion equivalent to one dose into a 250-milliliter volumetric flask. Add 200 milliliters of a solvent mixture of 95 percent ethanol and 0.1*M* phosphoric acid (8:2). Shake for 30 minutes on a wrist action shaker and dilute to volume with the solvent mixture. Centrifuge a portion of the sample solution for 10 minutes at 6,000 rpm. Use the clear supernatant without further dilution.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.

(4) *Identity.* Proceed as directed in § 436.330 of this chapter, except prepare the sample as follows: Reconstitute as directed in the labeling. Place 8.0 milliliters of the sample into a 100-milliliter volumetric flask, add 70 milliliters of 95 percent ethyl alcohol and shake for 30 minutes. Dilute to volume with 95 percent ethyl alcohol.

[47 FR 23711, June 1, 1982, as amended at 50 FR 19919, May 13, 1985]

### § 440.111 Carbenicillin indanyl sodium tablets.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Carbenicillin indanyl sodium tablets are composed of carbenicillin indanyl sodium and one or more suitable and harmless diluents, binders, lubricants, colorings, and coating substances. Each tablet contains carbenicillin indanyl sodium equivalent to 382 milligrams of carbenicillin. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of carbenicillin that it is represented to contain. Its moisture content is not more than 2.0 percent. It gives a positive identity test for carbenicillin indanyl sodium. The tablets shall disintegrate within 1 hour. The carbenicillin indanyl sodium used conforms to the standards prescribed by § 440.11(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The carbenicillin indanyl sodium used in making the batch for potency, moisture, pH, and identity.

(*b*) The batch for potency, moisture, identity, and disintegration time.

(ii) Samples required:

(*a*) The carbenicillin indanyl sodium used in making the batch: Five packages, each containing approximately 1 gram and one package containing approximately 2.5 grams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.300 of this chapter, except:

(i) *Preparation of the sample.* Accurately weigh 20 tablets and determine the average tablet weight. Using a mortar and pestle, grind the tablets to a fine powder. Accurately weigh a portion of the powder approximately equivalent to the weight of one tablet and transfer it into a 100-milliliter volumetric flask. Add approximately 70 milliliters of distilled water and shake the flask for 5 minutes. Dilute to volume and mix well. Transfer a 5-milliliter aliquot of the stock solution to a 50-milliliter glass-stoppered centrifuge tube. (The solution will be slightly turbid.) Add 15 milliliters of phosphate-citrate buffer and 20 milliliters of 4-methyl-2-pentanone to the tube. Stopper the tube and shake it for 10 seconds. Centrifuge at 2,000 revolutions per minute to separate the phases. Remove about 15 milliliters of the upper phase and proceed as directed in § 436.300(e) of this chapter.

(ii) *Calculations.* Calculate the carbenicillin content (potency) of the tablets as follows:

Milligrams of carbenicillin per tablet=(Degrees of rotation of sample solution × weight of working standard × average tablet weight × 100 × micrograms of carbenicillin in each milligram of the working standard)/(Degrees of rotation of working standard×weight of sample × 25 × 1,000)

where:

100 and 25=The volume of the sample and working standard solutions, respectively;

1,000=Factor to correct micrograms to milligrams.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Identity.* Proceed as directed in § 436.301 of this chapter, preparing the sample as follows: Using a mortar and pestle, grind a representative number of tablets into a fine powder. Dissolve a weighed amount of this powder in sufficient extraction solvent (described in § 436.301(b)(1) of this chapter) to give 10 milligrams of carbenicillin per milliliter. Shake the mixture for 5 minutes and promptly dilute an aliquot in extraction solvent to obtain a final concentration of 1 milligram carbenicillin per milliliter.

(4) *Disintegration time.* Proceed as directed in § 436.212 of this chapter, using the procedure described in paragraph (e)(2) of that section.

[39 FR 18976, May 30, 1974, as amended at 50 FR 19919, May 13, 1985]

## § 440.115 Cloxacillin sodium monohydrate oral dosage forms.

## § 440.115a Cloxacillin sodium monohydrate capsules.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Cloxacillin sodium monohydrate capsules are composed of cloxacillin sodium and one or more suitable and harmless diluents and lubricants. Each capsule contains cloxacillin sodium monohydrate equivalent to 125 milligrams, 250 milligrams, or 500 milligrams of cloxacillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cloxacillin that it is represented to contain. Its moisture content is not more than 5 percent. The cloxacillin sodium monohydrate used conforms to the standards prescribed by § 440.15(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''cloxacillin sodium capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The cloxacillin sodium monohydrate used in making the batch for potency, moisture, pH, cloxacillin content, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The cloxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedure.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of cloxacillin per milliliter (estimated).

(*b*) *Iodometric assay*. Proceed as directed in §436.204 of this subchapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this subchapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59861, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### §440.115b Cloxacillin sodium monohydrate for oral solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Cloxacillin sodium monohydrate for oral solution is a mixture of sodium cloxacillin with one or more suitable and harmless colorings, flavorings, buffer substances, and preservatives. When reconstituted as directed in the labeling, each milliliter contains the equivalent of 25 milligrams or 50 milligrams of cloxacillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cloxacillin that it is represented to contain. Its moisture content is not more than 1 percent. When reconstituted as directed in its labeling, its pH is not less than 5.0 nor more than 7.5. The cloxacillin sodium monohydrate used conforms to the standards prescribed by §440.15(a)(1).

(2) *Labeling.* In addition to the labeling requirements of §432.5 of this chapter, this drug shall be labeled ''cloxacillin sodium for oral solution''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The cloxacillin sodium monohydrate used in making the batch for potency, moisture, pH, cloxacillin content, identity, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The cloxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute the sample as directed in the labeling. Dilute an accurately measured representative aliquot of the sample with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of cloxacillin per milliliter (estimated).

(*b*) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this subchapter.

(3) *pH.* Proceed as directed in § 436.202 of this subchapter, using the drug reconstituted as directed in its labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59861, Nov. 22, 1977; 43 FR 9800, Mar. 10, 1978; 50 FR 19919, May 13, 1985]

### § 440.117 Cyclacillin oral dosage forms.

### § 440.117a Cyclacillin tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cyclacillin tablets are composed of cyclacillin with one or more suitable and harmless diluents, lubricants, colorings, and disintegrants. Each tablet contains 250 or 500 milligrams of cyclacillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cyclacillin that it is represented to contain. Its moisture content is not more than 5 percent. The tablets disintegrate within 15 minutes. It gives a positive identity test for cyclacillin. The cyclacillin used conforms to the standards prescribed by § 440.17(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The cyclacillin used in making the batch for potency, moisture, pH, cyclacillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, disintegration time, and identity.

(ii) Samples required:

(*a*) The cyclacillin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 3 to the reference concentration of 1.0 microgram of cyclacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample solution as follows: Place a representative number of tablets in a high-speed glass blender jar and add sufficient distilled water to give a convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot with distilled water to the prescribed concentration.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the potency of the sample as follows:

(*a*) *Preparation of working standard solution.* Dissolve and dilute an accurately weighed portion of the cyclacillin working standard in sufficient distilled water to obtain a concentration of 1.25 milligrams of cyclacillin per milliliter.

(*b*) *Preparation of sample solution.* Place one tablet into a high-speed glass blender jar and add sufficient distilled water to obtain a concentration of 1.25 milligrams of cyclacillin per milliliter. Blend for 3 to 5 minutes. Filter, if necessary.

(*c*) *Calculations.* Calculate the cyclacillin content in milligrams per tablet as follows:

$$\text{Milligrams of cyclacillin per 5 milliliters of sample} = \frac{A_u \times P_a \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Absorbance of sample solution;
$P_a$=Potency of working standard in micrograms per milliliter;
$A_s$=Absorbance of working standard solution;
$d$=Dilution factor of the sample.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter, using the procedure in paragraph (e)(1) of that section, except do not use discs.

(4) *Identity.* Proceed as directed in § 436.327 of this chapter, preparing the

sample as follows: Dissolve a representative portion of finely powdered tablets with sufficient 0.1*N* sodium hydroxide to obtain a solution containing 1 milligram of cyclacillin per milliliter. Allow the sample solution to stand for 15 minutes before using.

[46 FR 2985, Jan. 13, 1981; 46 FR 15880, Mar. 10, 1981, as amended at 50 FR 19919, May 13, 1985]

### §440.117b Cyclacillin for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cyclacillin for oral suspension is a mixture of cyclacillin with one or more suitable and harmless colorings, flavorings, buffer substances, sweetening ingredients, preservatives, and suspending agents. When reconstituted as directed in the labeling, it contains either 25 milligrams, 50 milligrams, or 100 milligrams of cyclacillin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cyclacillin that it is represented to contain. Its moisture content is not more than 1.5 percent. When reconstituted as directed in the labeling, its pH is not less than 4.5 and not more than 6.5. It gives a positive identity test for cyclacillin. The cyclacillin used conforms to the standards prescribed by §440.17(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The cyclacillin used in making the batch for potency, moisture, pH, cyclacillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, moisture, pH, and identity.

(ii) Samples required:

(*a*) The cyclacillin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of seven immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured representative portion of the sample into a suitable volumetric flask and dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a convenient concentration. Mix well. Further dilute an aliquot with solution 3 to the reference concentration of 1.0 microgram of cyclacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, preparing the sample as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured representative portion of the sample into an appropriate-sized volumetric flask and dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1). Mix well. Further dilute with solution 1 to the prescribed concentration.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in §442.40(b)(1)(ii) of this chapter, except prepare the working standard and sample solutions and calculate the potency of the sample as follows:

(*a*) *Preparation of working standard solution.* Dissolve and dilute an accurately weighed portion of the cyclacillin working standard in sufficient distilled water to obtain a concentration of 1.25 milligrams of cyclacillin per milliliter.

(*b*) *Preparation of sample solution.* Reconstitute the sample as directed in the labeling. Place an accurately measured aliquot of the sample into an appropriate-sized volumetric flask and dilute to volume with distilled water to yield a concentration of 1.25 milligrams of cyclacillin per milliliter. Mix well. Filter, if necessary.

(*c*) *Calculations.* Calculate the cyclacillin content as follows:

$$\text{Milligrams of cyclacillin per 5 milliliters of sample} = \frac{A_u \times P_a \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Absorbance of sample solution;

$P_a$=Potency of working standard in micrograms per milliliter;
$A_s$=Absorbance of working standard solution;
$d$=Dilution factor of the sample.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.

(4) *Identity.* Proceed as directed in § 436.327 of this chapter, preparing the sample as follows: Dilute an accurately measured representative portion of the reconstituted suspension with 0.1*N* sodium hydroxide to obtain a solution containing 1 milligram of cyclacillin per milliliter. Allow the sample solution to stand 45 minutes before using.

[46 FR 2985, Jan. 13, 1981; 46 FR 15880, Mar. 10, 1981, as amended at 50 FR 19919, May 13, 1985]

### § 440.119 Dicloxacillin sodium monohydrate oral dosage forms.

### § 440.119a Dicloxacillin sodium monohydrate capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Dicloxacillin sodium monohydrate capsules are composed of dicloxacillin sodium monohydrate and one or more suitable diluents and lubricants. Each capsule contains dicloxacillin sodium monohydrate equivalent to 62.5, 125, 250, or 500 milligrams of dicloxacillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of dicloxacillin that it is represented to contain. The moisture content is not more than 5 percent. The dicloxacillin sodium monohydrate conforms to the requirements of § 440.19(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''dicloxacillin sodium capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The dicloxacillin sodium monohydrate used in making the batch for potency, moisture, pH, organic chlorine content, free chloride content, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The dicloxacillin sodium monohydrate used in making the batch: 10 containers, each containing not less than 500 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 5.0 micrograms of dicloxacillin per milliliter (estimated) for the microbiological agar diffusion assay and to the prescribed concentration for the iodometric assay.

(ii) *Assay procedure.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter.

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59861, Nov. 22, 1977; 43 FR 2393, Jan. 17, 1978; 44 FR 10379, Feb. 20, 1979; 50 FR 19919, May 13, 1985]

### § 440.119b Dicloxacillin sodium monohydrate for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Dicloxacillin sodium monohydrate for oral suspension is a mixture of dicloxacillin sodium monohydrate with one or more suitable colorings, flavorings, buffer substances, and preservatives. When reconstituted as directed in the labeling, it contains the equivalent of 12.5 or 25 milligrams of dicloxacillin per milliliter. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of dicloxacillin that it is represented to contain. Its moisture content is not

more than 2 percent. The pH of the suspension, when reconstituted as directed in the labeling, is not less than 4.5 nor more than 7.5. The dicloxacillin sodium monohydrate used conforms to the requirements of §440.19(a)(1).

(2) *Labeling.* In addition to the labeling requirements of §432.5 of this chapter, this drug shall be labeled ''dicloxacillin sodium for oral suspension''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assay on:

(*a*) The dicloxacillin sodium monohydrate used in making the batch for potency, moisture, pH, organic chlorine content, free chloride content, crystallinity, and identity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The dicloxacillin sodium monohydrate used in making the batch: 10 containers, each containing not less than 500 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute the sample as directed in the labeling. Place an accurately measured aliquot of the sample containing an estimated 125 milligrams of dicloxacillin into a 100-milliliter volumetric flask. Add 20 milliliters of dimethylformamide and shake mechanically for 30 minutes. Dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1). The addition of dimethylformamide may be omitted if complete solution can be obtained with solution 1. Further dilute an aliquot with sufficient solution 1 to the reference concentration of 5.0 micrograms of dicloxacillin per milliliter (estimated) for the microbiological agar diffusion assay and to the prescribed concentration for the iodometric assay.

(ii) *Assay procedure.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter.

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59861, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### §440.125 Hetacillin oral dosage forms.

### §440.125a Hetacillin chewable tablets.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Each hetacillin chewable tablet contains an amount of hetacillin equivalent to 112.5 milligrams of ampicillin with suitable buffers, preservatives, binders, flavorings, colorings, and sweetening ingredients. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. The moisture content is not more than 2.0 percent. The hetacillin used conforms to the requirements of §440.25(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The hetacillin used in making the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required.

(*a*) The hetacillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed for ampicillin in §436.105 of this chapter, using the ampicillin working standard as the standard of comparison and preparing the sample for assay as follows: Place a

representative number of tablets in a high-speed glass blender with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 18976, May 30, 1974, as amended at 50 FR 19919, May 13, 1985]

### § 440.125b Hetacillin for oral suspension.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Hetacillin for oral suspension is a mixture of hetacillin with one or more suitable preservatives, suspending agents, sweetening ingredients, flavorings, and colorings. When reconstituted as directed in the labeling, it contains the equivalent of 22.5, 45, or 112.5 milligrams of ampicillin per milliliter. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its moisture content is not more than 2.0 percent. The pH of the suspension, when reconstituted as directed in its labeling, is not less than 2.0 and not more than 5.0. The hetacillin used conforms to the requirements of § 440.25(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The hetacillin used in making the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The hetacillin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed for ampicillin in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Remove an accurately measured representative portion with a suitable syringe and hypodermic needle and place into a suitable volumetric flask. Dilute to volume with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3). Further dilute an aliquot with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the sample after reconstituting as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 50 FR 19919, May 13, 1985]

### § 440.129 Hetacillin potassium capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Hetacillin potassium capsules are composed of potassium hetacillin with or without one or more suitable diluents, lubricants, and drying agents. Each capsule contains an amount of potassium hetacillin equivalent to 112.5, 225, or 450 milligrams of ampicillin. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. The moisture content is not more than 3 percent. The potassium hetacillin used conforms to the requirements of § 440.29(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The hetacillin potassium used in making the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The hetacillin potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed for ampicillin in §436.105 of this chapter, using the ampicillin working standard as the standard of comparison and preparing the sample for assay as follows: Place a representative number of capsules in a high-speed glass blender with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59861, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### §440.141 Nafcillin sodium monohydrate oral dosage forms.

### §440.141a Nafcillin sodium monohydrate tablets.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity*. Nafcillin sodium monohydrate tablets are composed of nafcillin sodium monohydrate with one or more suitable buffers, binders, disintegrants, diluents, and lubricants. Each tablet contains nafcillin sodium monohydrate equivalent to 500 milligrams of nafcillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of nafcillin that it is represented to contain. Its moisture content is not more than 5 percent. It shall disintegrate within 20 minutes. The nafcillin sodium monohydrate used conforms to the standards prescribed by §440.41(a)(1).

(2) *Labeling.* In addition to the labeling requirements of §432.5 of this chapter, this drug shall be labeled ''nafcillin sodium tablets''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The nafcillin sodium monohydrate used in making the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) The nafcillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation*. Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 2.0 micrograms of nafcillin per milliliter (estimated).

(*b*) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay*. Proceed as directed in §436.205 of this chapter.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in §436.212 of this chapter, using the method described in paragraph (e)(1) of that section, except use distilled water in lieu of simulated gastric fluid as the immersion fluid.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59862, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### § 440.141b Nafcillin sodium monohydrate capsules.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Nafcillin sodium monohydrate capsules are composed of nafcillin sodium monohydrate and one or more suitable and harmless buffer substances and lubricants. Each capsule contains nafcillin sodium monohydrate equivalent to 250 milligrams of nafcillin. The potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of nafcillin that it is represented to contain. The moisture content is not more than 5.0 percent. The nafcillin sodium monohydrate conforms to the standards prescribed by § 440.41(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''nafcillin sodium capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The nafcillin sodium monohydrate used in making the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The nafcillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 2.0 micrograms of nafcillin per milliliter (estimated) for the microbiological agar diffusion assay and to the prescribed concentration for the iodometric assay.

(ii) *Assay procedures.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter.

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59862, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### § 440.141c Nafcillin sodium monohydrate for oral solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Nafcillin sodium monohydrate for oral solution is a packaged combination of one immediate container of nafcillin sodium monohydrate and one immediate container of an aqueous diluent containing one or more suitable and harmless colorings, flavoring, buffers, dispersants, diluents, and preservatives. When reconstituted as directed in the labeling, each milliliter contains the equivalent of 50 milligrams of nafcillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of nafcillin that it is represented to contain. Its moisture content is not more than 5 percent. When reconstituted as directed in the labeling, its pH is not less than 5.5 and not more than 7.5. The nafcillin sodium monohydrate used conforms to the standards prescribed by § 440.41(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''nafcillin sodium for oral solution''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The nafcillin sodium monohydrate used in making the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The nafcillin sodium monohydrate used in making the

batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Place an accurately measured representative aliquot of the sample into a 250-milliliter volumetric flask and dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1). Mix well. Further dilute an aliquot with solution 1 to the reference concentration of 2.0 micrograms of nafcillin per milliliter (estimated) for the microbiological agar diffusion assay and to the prescribed concentration for the iodometric assay.

(ii) *Assay procedures.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter.

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59862, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### §440.149 Oxacillin sodium monohydrate oral dosage forms.

### §440.149a Oxacillin sodium monohydrate capsules.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Oxacillin sodium monohydrate capsules are composed of oxacillin sodium monohydrate with or without one or more diluents and lubricants, enclosed in a gelatin capsule. Each capsule contains oxacillin sodium monohydrate equivalent to 125, 250, or 500 milligrams of oxacillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of oxacillin that it is represented to contain. Its moisture content is not more than 6.0 percent. The oxacillin sodium monohydrate used conforms to the standards prescribed by §440.49(a)(1).

(2) *Labeling.* In addition to the labeling requirements of §432.5 of this chapter, this drug shall be labeled ''oxacillin sodium capsules''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The oxacillin sodium monohydrate used in making the batch for potency, moisture, pH, oxacillin content, crystallinity, and identity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The oxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of oxacillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59862, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### § 440.149b Oxacillin sodium monohydrate for oral solution.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Oxacillin sodium monohydrate for oral solution is a mixture of oxacillin sodium monohydrate with one or more suitable colorings, flavorings, buffer substances, stabilizers, and preservatives. When reconstituted as directed in the labeling, each milliliter contains the equivalent of either 25 or 50 milligrams of oxacillin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of oxacillin that it is represented to contain. Its moisture content is not more than 1.0 percent. When reconstituted as directed in its labeling, the pH of the solution is not less than 5.0 and not more than 7.5. The oxacillin sodium monohydrate used conforms to the standards prescribed by § 440.49(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''oxacillin sodium for oral solution''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The oxacillin sodium monohydrate used in making the batch for potency, moisture, pH, oxacillin content, crystallinity, and identity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The oxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Place an accurately measured representative aliquot of the sample into an appropriate-sized volumetric flask with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of oxacillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59862, Nov. 22, 1977; 50 FR 19919, May 13, 1985]

### § 440.155 Penicillin G benzathine oral dosage forms.

### §§ 440.155a—440.155b [Reserved]

### § 440.155c Penicillin G benzathine oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G benzathine oral suspension contains penicillin G benzathine with one or more suitable dispersing agents, buffer substances, preservatives, colorings, and flavorings. Each milliliter contains penicillin G benzathine equivalent to 30,000 units or 60,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its pH is not less than 6.0 and not more than 7.0. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

*(b)* The batch for potency and pH.

(ii) Samples required:

*(a)* The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch: A minimum of 5 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately measured representative volume of the sample in sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter, using a representative aliquot of the drug prepared for assay as described in paragraph (b)(2) of that section.

(2) *pH*. Proceed as directed in § 436.202 of this chapter, using the undiluted sample.

[42 FR 59862, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.155d Penicillin G benzathine tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Penicillin G benzathine tablets contain penicillin G benzathine with one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. Each tablet contains penicillin G benzathine equivalent to 200,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its moisture content is not more than 8.0 percent. The tablets shall disintegrate within 1 hour. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

*(b)* The batch for potency, moisture, and disintegration time.

(ii) Samples required:

*(a)* The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*. Using the penicillin G working standard as the standard of comparison, assay for potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing 200 milliliters of absolute methyl alcohol. Blend for 1 minute. Add an additional 300 milliliters of absolute methyl alcohol and blend again for 2 to 3 minutes. Immediately further dilute an aliquot with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Weigh and finely powder six tablets. Transfer two accurately weighed portions of the tablets, each equivalent to 200,000 units of penicillin G, to two separate 100-milliliter volumetric flasks. Dilute one flask, which is to be used as the blank, to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), and proceed as directed in § 436.204(d) of this chapter. In lieu of directions in § 436.204(e) (1), (2), and (3), to the other

flask add 10 milliliters of 1.0*N* NaOH and mix well. Allow to stand for 15 minutes, then add 10 milliliters of 1.2*N* HC1, and dilute to volume with distilled water. Pipette a 2.0-milliliter aliquot into a 125-milliliter glass-stoppered Erlenmeyer flask and proceed as directed in § 436.204(c)(4) of this chapter.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter.

[42 FR 59862, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.171 Penicillin V oral dosage forms.

### § 440.171a Penicillin V capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V capsules are composed of penicillin V with one or more suitable and harmless lubricants. Each capsule contains either 125 milligrams (200,000 units) or 250 milligrams (400,000 units) of penicillin V. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 2 percent. The penicillin V used conforms to the standards prescribed by § 440.71(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin V used in making the batch for potency, moisture, pH, penicillin V content, and crystallinity.

*(b)* The batch for potency and moisture.

(ii) Samples required:

*(a)* The penicillin V used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient absolute methyl alcohol to give a solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter. Immediately dilute an aliquot of the methyl alcohol solution with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the methyl alcohol with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[42 FR 59863, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.171b Penicillin V for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V for oral suspension is composed of penicillin V with or without one or more suitable and harmless suspending agents, colorings, flavorings, and buffer substances. When reconstituted as directed in the labeling, each millilter contains 25 milligrams (40,000 units), 50 milligrams (80,000 units) or 208.3 milligrams (333,333 units) of penicillin V. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 2.0 and not more than 4.0. The penicillin V used conforms to the standards prescribed by § 440.71(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin V used in making the batch for potency, moisture, pH, penicillin V content, and crystallinity.

*(b)* The batch for potency, moisture, and pH.

(ii) Samples required:

*(a)* The penicillin V used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Dissolve an accurately measured representative volume of the sample in sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately further dilute an aliquot with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V (estimated).

(ii) *Iodometric assay*. Proceed as directed in §436.204 of this chapter, preparing the sample as follows: Reconstitute as directed in the labeling. Dissolve an accurately measured representative portion of the sample in absolute methyl alcohol and dilute with 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1) to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the sample reconstituted as directed in the labeling.

[42 FR 59863, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### §440.171c Penicillin V tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Penicillin V tablets are composed of penicillin V with or without one or more suitable and harmless diluents, binders, lubricants, and colorings. Each tablet contains 125 milligrams (200,000 units), 300 milligrams (500,000 units), or 500 milligrams (800,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 3 percent. It shall disintegrate within 1 hour. The penicillin V used conforms to the standards prescribed by §440.71(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin V used in making the batch for potency, moisture, pH, penicillin V content, and crystallinity.

*(b)* The batch for potency, moisture, and disintegration time.

(ii) Samples required:

*(a)* The penicillin V used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient absolute methyl alcohol to give a stock solution of convenient concentration. Blend for 2 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter. Immediately dilute an aliquot of the methyl alcohol solution with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

*(b) Iodometric assay*. Proceed as directed in §436.204 of this chapter, diluting an aliquot of the methyl alcohol solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in §436.212 of this chapter.

[42 FR 59864, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.173 Penicillin V potassium oral dosage forms.

### § 440.173a Penicillin V potassium capsules.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium capsules are composed of penicillin V potassium and one or more suitable lubricants and fillers. Each capsule contains penicillin V potassium equivalent to 250 milligrams (400,000 units) or 500 milligrams (800,000 units) of penicillin V. The potency is satisfactory if it is not less than 90 percent and more than 115 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its loss on drying is not more than 2.0 percent. The penicillin V potassium used conforms to the standards prescribed by § 440.73(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V potassium used in making the batch for potency, loss on drying, pH, crystallinity, penicillin V content.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Using the penicillin V working standard as the standard of comparison, assay by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

[42 FR 59864, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.173b Penicillin V potassium chewable tablets.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium chewable tablets are composed of penicillin V potassium with suitable diluents, binders, buffers, colorings, and flavorings. Each tablet contains penicillin V potassium equivalent to 125 milligrams (200,000 units) or 250 milligrams (400,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams or units of penicillin V that it is represented to contain. The loss on drying is not more than 1.5 percent. The penicillin V potassium used conforms to the standards prescribed by § 440.73(a) (1).

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled ''penicillin V potassium tablets''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V potassium used in making the batch for potency, loss on drying, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

[42 FR 59864, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### §440.173c Penicillin V potassium tablets.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium tablets are composed of penicillin V potassium with or without one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains penicillin V potassium equivalent to 125 milligrams (200,000 units), 250 milligrams (400,000 units), or 500 milligrams (800,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its loss on drying is not more than 1.5 percent. It shall disintegrate within 1 hour. The penicillin V potassium used conforms to the standards prescribed by §440.73(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V potassium used in making the batch for potency, loss on drying, pH, penicillin V content and crystallinity.

(*b*) The batch for potency, loss on drying, and disintegration time.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescibed concentration.

(2) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

(3) *Disintegration time.* Proceed as directed in §436.212 of this chapter.

[42 FR 59865, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### §440.173d Penicillin V potassium for oral solution.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium for oral solution is composed of penicillin V potassium with or without one or more suitable and harmless suspending agents, colorings, flavorings, buffer substances, and preservatives. When reconstituted as directed in the labeling, each milliliter contains penicillin V potassium equivalent to either 25 milligrams (40,000 units) or 50 milligrams

(80,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 135 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin V potassium used conforms to the standards prescribed by §440.73(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such requests shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin V potassium used in making the batch for potency, loss on drying, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Dilute an accurately measured representative portion of the suspension with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the sample when reconstituted as directed in the labeling.

[42 FR 59865, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### §440.180 Penicillin G potassium oral dosage forms.

### §440.180a Penicillin G potassium tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin potassium tablets are composed of penicillin G potassium with or without one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains penicillin G potassium equivalent to 100,000 units, 200,000 units, 250,000 units, 400,000 units, 500,000 units, 800,000 units or 1,000,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its loss on drying is not more than 1 percent. The tablets shall disintegrate within 1 hour. The penicillin G potassium used conforms to the standards prescribed by §440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: Potency, loss on drying, and disintegration time of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed or the manufacturer has submitted to the Commissioner, and it has been accepted, information adequate to prove that such tests are not necessary, loss on

drying of the tablets collected during each day of packaging the batch.

(*2*) If the person who requests certification is not the manufacturer of the batch: Potency, loss on drying, and disintegration time of tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch:

*(1)* If the person who requests certification is the manufacturer of the batch: A minimum of 36 tablets. If, after tableting, such person packaged the batch into dispensing-size containers: 20 tablets, collected at equal intervals during each day the tablets are being packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed or if the manufacturer has been exempted by the Commissioner from such requirement.

*(2)* If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filled by such person into dispensing-size containers during each day's packaging operations): A minimum of 36 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets so that the quantities packaged during the intervals are approximately equal.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter.

[42 FR 59865, Nov. 22, 1977; 43 FR 3705, Jan. 27, 1978, as amended at 50 FR 19919, May 13, 1985]

### § 440.180c Penicillin G potassium capsules.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium capsules are composed of penicillin G potassium and a suitable and harmless diluent. Each capsule contains penicillin G potassium equivalent to 250,000 units or 400,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its loss on drying is not more than 1.5 percent. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

*(a)* The penicillin G potassium used in making the batch for potency, loss on drying, pH, penicillin G content, and crystallinity.

*(b)* The batch:

*(1)* If the person who requests certification is the manufacturer of the batch: Potency and loss on drying of capsules collected during the time of encapsulating the batch; and, unless the capsules are packaged into dispensing-size containers immediately after they are encapsulated or the manufacturer has submitted to the Commissioner, and it has been accepted, information adequate to prove that such tests are not necessary, loss on drying of capsules collected during each day of packaging the batch.

*(2)* If the person who requests certification is not the manufacturer of the batch: Potency and loss on drying of capsules collected during each day the capsules are being packaged into dispensing-size containers.

(ii) Samples required:

*(a)* The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

*(b)* The batch:

*(1)* If the person who requests certification is the manufacturer of the batch: A minimum of 30 capsules. If after encapsulating, such person packaged the batch into dispensing-size containers: 20 capsules collected at equal intervals during each day the capsules are being packaged, except that this sample is not required if the capsules are packaged immediately after they are filled or if the manufacturer has been exempted by the Commissioner from such requirement.

*(2)* If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of capsules filed by such person into dispensing-size containers during each day's packaging operations): A minimum of 30 capsules collected by taking single capsules at such intervals throughout each day of packaging the capsules that the quantities packaged during the intervals are approximately equal.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

[42 FR 59866, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.180f Penicillin G potassium for oral solution.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium for oral solution contains penicillin G potassium and one or more suitable and harmless buffers, colorings, flavorings, diluents, and preservatives. Each milliliter contains penicillin G potassium equivalent to 20,000 units, 25,000 units, 40,000 units, 50,000 units, 80,000 units, or 100,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of units of penicillin G that it is represented to contain. Its moisture content is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 5.5 and not more than 7.5. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Transfer an accurately measured representative portion into a suitable volumetric

flask and dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1).

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the solution obtained after reconstituting the drug as directed in the labeling.

[42 FR 59866, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.180g Penicillin G potassium tablets for solution.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium tablets for solution are composed of penicillin G potassium. Each tablet contains penicillin G potassium equivalent to 100,000 units, 200,000 units, or 250,000 units of penicillin G. The potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its loss on drying is not more than 1 percent. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: Potency and loss on drying of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed, or the manufacturer has submitted to the Commissioner, and it has been accepted, information adequate to prove that such tests are not necessary, loss on drying of the tablets collected during each day of packaging the batch.

(*2*) If the person who requests certification is not the manufacturer of the batch: Potency and loss on drying of the tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: A minimum of 30 tablets. If, after tableting, such person packaged the batch into dispensing-size containers: 20 tablets collected at equal intervals during each day the tablets are packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed or if the manufacturer has been exempted by the Commissioner from such requirement.

(*2*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filed by such person into dispensing-size containers during each day's packaging operations): A minimum of 30 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets that the quantities packaged during the intervals are approximately equal.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

[42 FR 59867, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

## Subpart C—Injectable Dosage Forms

### § 440.201 Sterile azlocillin sodium.

The requirements for certification and the tests and methods of assay for sterile azlocillin sodium packaged for dispensing are described in § 440.1a.

[47 FR 53349, Nov. 26, 1982]

### § 440.202 Sterile amdinocillin.

The requirements for certification and the tests and methods of assay for sterile amdinocillin packaged for dispensing are described in § 440.2a.

[50 FR 7766, Feb. 26, 1985]

### § 440.207 Sterile ampicillin trihydrate for suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile ampicillin trihydrate for suspension is a dry mixture of ampicillin trihydrate and one or more suitable and harmless buffer substances, stabilizers, suspending agents, and preservatives. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not less than 11.4 percent and not more than 14.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.0. The ampicillin trihydrate used conforms to the standards prescribed by § 440.7a(a)(1) of this chapter.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled ''sterile ampicillin for suspension.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(*b*) The batch for potency, sterility, pyrogens, loss on drying, and pH.

(ii) Samples required:

(*a*) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 12 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container, or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the resultant solution with 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), for the microbiological agar diffusion assay, or distilled water for the iodometric assay, to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter.

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2*N* hydrochloric acid to both the sample and working standard solutions after the addition of 0.01*N* iodine solution. Dilute an aliquot of the stock solution with distilled water to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except in lieu of (e)(1)(i)(*a*), prepare the sample for test as follows: From each of 10 immediate containers, aseptically transfer approximately 300 milligrams of sample into a sterile 500-milliliter Erlenmeyer flask containing approximately 400 milliliters of diluting fluid D. Add at least 200,000 Levy units[1] of penicillinase. Repeat the process using 10 additional containers. Swirl both of the stoppered flasks to completely solubilize the suspension prior to filtration and proceed as directed in paragraph (e)(1)(ii) of that section. If the formulation cannot be filtered, proceed as directed in § 436.20(e)(2) of this chapter, except use medium B in lieu of medium A.

(3) *Pyrogens.* Proceed as directed in § 436.32(f) of this chapter, using a solution containing 20 milligrams of ampicillin per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using the solution obtained when the product is reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3459, Jan. 27, 1984; 50 FR 19918, 19919, May 13, 1985]

### § 440.209 Ampicillin sodium injectable dosage forms.

### § 440.209a Sterile ampicillin sodium.

The requirements for certification and the tests and methods of assay for sterile ampicillin sodium packaged for dispensing are described in § 440.9a.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59867, Nov. 22, 1977. Redesignated at 52 FR 42288, Nov. 4, 1987]

### § 440.209b Sterile ampicillin sodium and sulbactam sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin sodium and sulbactam sodium is a dry mixture of ampicillin sodium and sulbactam sodium in which the ratio of ampicillin to sulbactam is 2:1. Its ampicillin potency is not less than 563 micrograms of ampicillin per milligram on an anhydrous basis. It contains not less than 280 micrograms of sulbactam per milligram on an anhydrous basis. Its ampicillin sodium content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of ampicillin that it is represented to contain. Its sulbactam sodium content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of sulbactam that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 2.0 percent. The pH of an aqueous solution containing 10 milligrams of ampicillin and 5 milligrams of sulbactam per milliliter is not less than 8.0 and not more than 10.0. It passes the identity test for ampicillin and sulbactam. The ampicillin sodium content conforms to the standards prescribed by § 440.9a(a)(1) of this chapter. The sulbactam content conforms to the standards prescribed by § 455.82a(a)(1) of this chapter.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The ampicillin sodium used in making the batch for potency, sterility, pyrogens, moisture, pH, crystallinity, and identity.

(B) The sulbactam sodium used in making the batch for potency, sterility, pyrogens, moisture, crystallinity, and identity.

[1] One Levy unit of penicillinase inactivates 59.3 units of pencillin G in 1 hour at 25° C. and at a pH of 7.0 in a phosphate buffered solution of a pure alkali salt of penicillin G when the substrate is in sufficient concentration to maintain a zero order reaction.

(C) The batch for ampicillin potency, sulbactam potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The ampicillin sodium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(B) The sulbactam sodium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(C) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: A minimum of 20 immediate containers collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Ampicillin and sulbactam content.* Proceed as directed in §436.216 of this chapter, operating isothermally at 25 °C, using an ultraviolet detection system operating at a wavelength of 230 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silica, a flow rate of 2.0 milliliters per minute, and a known injection volume of 10 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(A) *1.0M Phosphoric acid.* Prepare by diluting 67.5 milliliters of reagent grade phosphoric acid (85 percent) in distilled water to 1 liter.

(B) *0.005M Tetrabutylammonium hydroxide.* Dilute 6.6 milliliters of tetrabutylammonium hydroxide (40 percent) to 1,800 milliliters with distilled water. Adjust the pH to 5.0 with 1.0*M* phosphoric acid and dilute with distill water to 2 liters.

(C) *Mobile phase.* Mix 350 milliliters of acetonitrile with 1,650 milliliters of 0.005*M* tetrabutylammonium hydroxide. Filter and degas the mobile phase just prior to its introduction into the chromatograph pumping system. (Slight adjustments in pH and/or acetonitrile content may be made to achieve the system suitability parameters defined in paragraph (b)(1)(iii) of this section.)

(ii) *Preparation of working standard and sample solutions*—(A) *Working standard solution.* Accurately weigh a portion of the ampicillin working standard containing the equivalence of approximately 75 milligrams of ampicillin activity and transfer into a 25-milliliter volumetric flask. Accurately weigh a portion of the sulbactam working standard containing 35 milligrams of sulbactam and transfer into the 25-milliliter volumetric flask containing the ampicillin. Dissolve and dilute to volume with mobile phase. Further dilute 5 milliliters to 25 milliliters with mobile phase.

(B) *Sample solution.* Dissolve an accurately weighed sample in sufficient mobile phase to give a stock solution containing 1 milligram of sample per milliliter (estimated); and, also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container, or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with mobile phase to yield a solution containing about 0.30 milligram sulbactam and about 0.60 milligram ampicillin per milliliter.

(iii) *System suitability requirements*—(A) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5 at 10 percent of peak height in lieu of 5 percent of peak height.

(B) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 3,500 theoretical plates for sulbactam for a 30-centimeter column.

(C) *Resolution.* Dissolve 17.5 milligrams of sulbactam in 50 milliliters of 0.01*N* sodium hydroxide and let stand for 30 minutes. Adjust the pH of the solution to 5.0 with concentrated phosphoric acid. Transfer a 5-milliliter aliquot of the resulting solution to a 25-milliliter volumetric flask, add 4.25 milliliters of acetonitrile, and dilute to volume with 0.005*M* tetrabutylammonium hydroxide as described in paragraph (b)(1)(i)(B) of this section. Transfer 2 milliliters of this solution to a 50-milliliter flask, add 30

milligrams of ampicillin potency, dissolve and dilute to volume with mobile phase. Use this solution to determine the resolution factor. The resolution ($R$) between the peaks for ampicillin and sulbactam alkaline degradation product is satisfactory if it is not less than 1.2.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation ($S_R$ in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in § 436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are comparable to the system. However, the sample preparation described in paragraph (b)(1)(ii)(*b*) of this section should not be changed.

(iv) *Calculations.* (A) Calculate the micrograms of ampicillin or sulbactam per milligram of sample as follows:

$$\text{Micrograms of ampicillin or sulbactam per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}$$

where:

$A_u$=Area of the ampicillin or sulbactam peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ampicillin or sulbactam peak in the chromatogram of the ampicillin or sulbactam working standard;

$P_s$=Ampicillin or sulbactam activity in the ampicillin-sulbactam working standard solution in micrograms per milliliter;

$C_u$=Milligrams of sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(B) Calculate the ampicillin or sulbactam content of the container as follows:

$$\text{Milligrams of ampicillin or sulbactam per container} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Area of the ampicillin or sulbactam peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ampicillin or sulbactam peak in the chromatogram of the ampicillin or sulbactam working standard;

$P_s$=Ampicillin or sulbactam activity in the ampicillin-sulbactam working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20 milligrams of sulbactam and 40 milligrams of ampicillin per milliliter.

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams of ampicillin and 5 milligrams of sulbactam per milliliter.

(6) *Identity.* The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ampicillin-sulbactam working standard.

[52 FR 42288, Nov. 4, 1987, as amended at 54 FR 47205, Feb. 20, 1989; 55 FR 11582, Mar. 29, 1990]

### § 440.210 Benzylpenicilloyl-polylysine injection.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Benzylpenicilloyl-polylysine injection is an aqueous solution of benzylpenicilloyl-polylysine. It contains one or more suitable and harmless buffers. Its benzylpenicilloyl content is satisfactory if it is not less than $5.4\times10^{-5}M$ and not more than $7.0\times10^{-5}M$, except that for the issuance of a certificate for a batch, the benzylpenicilloyl content must be not less than $6.4\times10^{-5}M$. It is sterile. It is nonpyrogenic. Its pH is not less than 6.5 and not more than 8.5. The benzylpenicilloyl-polylysine concentrate used conforms to the standards prescribed by § 440.10(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The benzylpenicilloyl-polylysine concentrate used in making the batch for percent benzylpenicilloyl substitution, benzylpenicilloyl content, penamaldate content, penicillenate content, and pH.

(*b*) The batch for benzylpenicilloyl content, sterility, pyrogens, and pH.

(ii) Samples required:

(*a*) The benzylpenicilloyl-polylysine concentrate used in making the batch: 2 vials, each containing not less than 5 milliliters.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 60 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Benzylpenicilloyl content.* Proceed as directed in § 440.10(b)(1)(ii) except in lieu of § 440.10(b)(1)(ii)(*b*) prepare the sample solution as follows: Pool contents of 16 immediate containers. Dilute a 3.0-milliliter aliquot to 10 milliliters with saline phosphate buffer, pH 7.6.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, preparing the sample solution as follows: Pool the contents of at least 8 vials to obtain a minimum of 1.5 milliliters of the original preparation. Dilute the 1.5 milliliters to 50 milliliters with diluent 2.

(4) [Reserved]

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

[39 FR 35347, Oct. 1, 1974, as amended at 42 FR 14094, Mar. 15, 1977; 50 FR 19918, 19919, May 13, 1985]

### § 440.213 Sterile carbenicillin disodium.

The requirements for certification and the tests and methods of assay for sterile carbenicillin disodium packaged for dispensing are described in § 440.13a.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59867, Nov. 22, 1977]

### § 440.219 Dicloxacillin sodium monohydrate injectable dosage forms.

### § 440.219a Sterile dicloxacillin sodium monohydrate.

The requirements for certification and the tests and methods of assay for sterile dicloxacillin sodium monohydrate packaged for dispensing are described in § 440.19a.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59867, Nov. 22, 1977]

### § 440.219b Dicloxacillin sodium monohydrate for injection.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Dicloxacillin sodium monohydrate for injection is a dry mixture of dicloxacillin sodium monohydrate and lidocaine hydrochloride packaged for dispensing. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of dicloxacillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 5 percent. When reconstituted as directed in the labeling, its pH is not less than 4.5 and not more than 7.5. The dicloxacillin sodium monohydrate used conforms to the standards prescribed by § 440.19a(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''dicloxacillin sodium for injection''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The dicloxacillin sodium monohydrate used in making the batch for potency, moisture, pH, organic chlorine content, free chloride content, crystallinity, and identity.

(*b*) The batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) The dicloxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the sample thus obtained with sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay or in distilled water for the iodometric assay and hydroxylamine colorimetric assay, to give a stock solution of convenient concentration.

(ii) *Assay procedure.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of dicloxacillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with distilled water to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, except dilute an aliquot of the stock solution with distilled water to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 20 milligrams of dicloxacillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using the product reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59867, Nov. 22, 1977; 50 FR 19918, 19919, May 13, 1985]

### § 440.229 Hetacillin potassium injectable dosage forms.

### § 440.229a Sterile hetacillin potassium.

The requirements for certification and the tests and methods of assay for sterile hetacillin potassium packaged for dispensing are described in § 440.29a.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59867, Nov. 22, 1977]

### § 440.229b Hetacillin potassium for injection.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Hetacillin potassium for injection is a dry mixture of hetacillin potassium and lidocaine hydrochloride. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. It is sterile and nonpyrogenic. Its moisture content is not more than 1.0 percent. When reconstituted as directed in its labeling, its pH is not less than 7.0 and not more than 9.0. The hetacillin potassium used conforms to the requirements of § 440.29a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The hetacillin potassium used in making the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) The hetacillin potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers,

except if each contains less than 450 milligrams of ampicillin, a minimum of 16 immediate containers.

(*2*) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed for ampicillin in § 436.105 of this chapter, using the ampicillin working standard as the standard of comparison and preparing the sample for assay as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove the withdrawable contents from each container represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, withdraw an accurately measured representative portion from each container. Dilute the sample thus obtained with sufficient 0.1*M* potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Further dilute the stock solution with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens*. Proceed as directed in § 436.32(a) of this chapter, using a solution containing the equivalent of 18 milligrams of ampicillin per milliliter.

(4) [Reserved]

(5) *Moisture*. Proceed as directed in § 436.201 of this chapter.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using the product reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59867, Nov. 22, 1977; 50 FR 19918, 19919, May 13, 1985]

### § 440.236 Methicillin sodium monohydrate for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Methicillin sodium monohydrate for injection is methicillin sodium monohydrate with or without one or more suitable and harmless preservatives and the buffer sodium citrate in a quantity not less than 4 percent and not more than 5 percent by weight of its total solids (such sodium citrate conforms to the standards prescribed therefor by the U.S.P.). Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of methicillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 6.0 and not more than 8.5. Its moisture content is not more than 6.0 percent. The methicillin sodium monohydrate used conforms to the standards prescribed by § 440.36a(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''methicillin sodium for injection''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The methicillin sodium monohydrate used in making the batch for potency, moisture, pH, methicillin content, crystallinity, and identity.

(*b*) The batch for potency, sterility, pyrogens, pH, and moisture.

(ii) Samples required:

(*a*) The methicillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams, plus one package containing approximately 2 grams.

(*b*) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation*. Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the portion thus obtained with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give

a stock solution of convenient concentration.

(ii) *Assay procedure.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this subchapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 10 micrograms of methicillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this subchapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in §436.20 of this subchapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(a) of this chapter, using a solution containing 60 milligrams of methicillin per milliliter.

(4) [Reserved]

(5) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per millilter.

(6) *Moisture.* Proceed as directed in §436.201 of this subchapter.

[39 FR 18976, May 30, 1974, as amended at 40 FR 15089, Apr. 4, 1975; 42 FR 59868, Nov. 22, 1977; 49 FR 5096, Feb. 10, 1984; 50 FR 19918, 19919, May 13, 1985]

### §440.237 Sterile mezlocillin sodium monohydrate.

The requirements for certification and the tests and methods of assay for sterile mezlocillin sodium monohydrate packaged for dispensing are described in §440.37a.

[46 FR 58299, Dec. 1, 1981]

### §440.241 Nafcillin sodium injectable dosage forms.

### §440.241a Nafcillin sodium monohydrate for injection.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Nafcillin sodium monohydrate for injection is a dry mixture of nafcillin sodium monohydrate and a suitable buffer substance. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of nafcillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not less than 3.5 and not more than 5.3 percent. When reconstituted as directed in the labeling, the pH is not less than 6.0 and not more than 8.5. The nafcillin sodium monohydrate used conforms to the requirements of §440.41a(a)(1).

(2) *Labeling.* In addition to the labeling requirements of §432.5 of this chapter, this drug shall be labeled ''nafcillin sodium for injection''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The nafcillin sodium monohydrate used in making the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity.

(*b*) The batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) The nafcillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 12 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation remove an accurately measured representative portion from each container. Dilute the sample thus obtained with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 2.0 micrograms of nafcillin per milliliter (estimated) for the microbiological agar diffusion assay and to the prescribed concentration for the iodometric assay.

(ii) *Assay procedures.* Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter.

(*b*) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 80 milligrams of nafcillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using the solution obtained when the product is reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59868, Nov. 22, 1977; 45 FR 22922, Apr. 4, 1980; 47 FR 22515, May 25, 1982; 50 FR 19919, May 13, 1985. Redesignated at 55 FR 277, Jan. 4, 1990]

### § 440.241b Nafcillin sodium injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Nafcillin sodium injection is a frozen, aqueous, iso-osmatic solution of nafcillin sodium which may contain one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains nafcillin sodium equivalent to 20 or 40 milligrams of nafcillin. Its nafcillin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of nafcillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 6.0 and not more than 8.5. The nafcillin sodium monohydrate used conforms to the standards prescribed by § 440.41(a)(1).

(2) *Labeling.* it shall be labeled in accordance with the requirements of § 432.5 of this chapter. In addition, this drug shall be labeled ''nafcillin sodium injection.''

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The nafcillin sodium monohydrate used in making the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity.

(B) The batch for nafcillin content, sterility, pyrogens, and pH.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The nafcillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*. Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Nafcillin content.* Proceed as directed in § 440.241a(b)(1), except use the thawed solution.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 80 milligrams of nafcillin per kilogram.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

[55 FR 277, Jan. 4, 1990]

### § 440.249 Oxacillin sodium injectable dosage forms.

### § 440.249a Oxacillin sodium monohydrate for injection.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity*. Oxacillin sodium monohydrate for injection is a dry mixture of oxacillin sodium monohydrate and one or more buffer substances, with or without trisodium ethylenediamine tetraacetic acid, and with or without one or more suitable and harmless preservatives. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of

the number of milligrams of oxacillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 6.0 percent. Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 6.0 and not more than 8.5. The oxacillin sodium monohydrate used conforms to the standards prescribed by § 440.49a(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled ''oxacillin sodium for injection''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The oxacillin sodium monohydrate used in making the batch for potency, moisture, pH, oxacillin content, crystallinity, and identity.

(*b*) The batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) The oxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation, or 40 immediate containers if each contains less than 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container, or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 5 micrograms of oxacillin per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 20 milligrams of oxacillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 30 milligrams per milliliter.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59868, Nov. 22, 1977; 50 FR 19918, 19919, May 13, 1985. Redesignated at 55 FR 279, Jan. 4, 1990]

### § 440.249b Oxacillin sodium injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxacillin sodium injection is a frozen aqueous, iso-osmotic solution of oxacillin sodium which may contain one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains oxacillin sodium equivalent to 20 or 40 milligrams of oxacillin. Its oxacillin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of oxacillin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 6.0 and not more than 8.5. The oxacillin sodium monohydrate used conforms to the standards prescribed by § 440.49(a)(1), except that the pH of an aqueous solution containing 30 milligrams per milliliter is not less than 4.0 and not more than 7.0.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter. In addition, this

drug shall be labeled ''oxacillin sodium injection''.

(3) *Requests for certification: samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The oxacillin sodium monohydrate used in making the batch for potency, moisture, pH, oxacillin content, crystallinity, and identity.

(B) The batch for oxacillin content, sterility, pyrogens, and pH.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The oxacillin sodium monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Thaw the sample as directed in the labeling. he sample solution used for testing must be at room temperature.

(1) *Oxacillin content.* Proceed as directed in §440.249a(b)(1), except use the thawed solution.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 20 milligrams of oxacillin per kilogram.

(4) *pH.* Proceed as directed in §436.202 of this chapter, using the undiluted solution.

[55 FR 279, Jan. 4, 1990; 55 FR 2481, Jan. 24, 1990]

### §440.255 Penicillin G benzathine injectable dosage forms.

### §440.255b Sterile penicillin G benzathine suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G benzathine suspension is an aqueous suspension of penicillin G benzathine and one or more suitable suspending or dispersing agents, buffer substances, and preservatives. Each container or each milliliter contains penicillin G benzathine equivalent to not less than 300,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5. The penicillin G benzathine used conforms to the standards prescribed by §440.55a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, and pH.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filing operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dilute the portion thus obtained with sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately further dilute with 1 percent

potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay*. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Using the sample thus obtained, proceed as directed in §436.204(b)(2) of this chapter.

(2) *Sterility*. Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, and medium F in lieu of medium E. During the period of incubation, shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in §436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *pH*. Proceed as directed in §436.202 of this chapter, using the undiluted sample.

[42 FR 59868, Nov. 22, 1977, as amended at 43 FR 9799, Mar. 10, 1978; 50 FR 19918, 19919, May 13, 1985]

### §440.255c Sterile penicillin G benzathine-penicillin G procaine suspension.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity*. Sterile penicillin G benzathine-penicillin G procaine suspension is an aqueous mixture of penicillin G benzathine and penicillin G procaine with or without suitable and harmless buffer substances, suspending agents, and preservatives. Each container or each milliliter contains penicillin G benzathine and penicillin G procaine each equivalent to not less than 150,000 units of penicillin G. Its penicillin G benzathine content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. Its penicillin G procaine content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5. The penicillin G benzathine used conforms to the standards prescribed by §440.55a (a)(1). The penicillin G procaine used conforms to the standards prescribed by §440.74a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The penicillin G procaine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*c*) The batch for penicillin G benzathine content, penicillin G procaine content, sterility, pyrogens, and pH.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regualr intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Total potency*. Assay for total potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, place one dose of the drug in a 100-milliliter volumetric flask and add sufficient methyl alcohol to dissolve the benzathine penicillin G. Dilute to volume with 1 percent potassium phosphate buffer, pH 6.0

(solution 1), and shake well. Immediately further dilute an aliquot with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, withdraw 2 one-dose portions of sample. Place one portion into an appropriate-sized volumetric flask and add 20 milliliters of 0.5*N* NaOH for each 300,000 units of benzathine penicillin G, mix well, being sure that all penicillin is in solution, and allow to stand for 15 minutes. Add 1 milliliter of 1.2*N* HCl for each 2 milliliters of 0.5*N* NaOH, mix, and dilute with distilled water to obtain a concentration of 2,000 units per milliliter. Dilute the other portion, which is to be used as the blank solution, with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a concentration of approximately 2,000 units per milliliter.

(ii) *Penicillin G procaine content—(a) Reagents—(1) Sodium nitrite solution.* Dissolve 0.1 gram of sodium nitrite in 100 milliliters of distilled water. Prepare a fresh solution every week and store under refrigeration.

*(2) Ammonium sulfamate solution.* Dissolve 0.5 gram of ammonium sulfamate in 100 milliliters of distilled water and store under refrigeration.

*(3) N-(1-naphthyl)-ethylenediamine solution.* Dissolve 0.1 gram of *N*-(1-naphthyl) - ethylenediamine dihydrochloride in 100 milliliters of distilled water. Prepare fresh solutions every week and store under refrigeration.

*(4) Standard procaine solution.* Prepare a standard solution containing 27.55 milligrams of procaine hydrochloride U.S.P. in a liter of distilled water (each milliliter of the standard solution is equivalent to 60 units of penicillin G procaine).

(*b*) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, withdraw a one-dose portion of the sample and place it into an appropriate-sized volumetric flask. Add 20 milliliters of 0.5*N* NaOH for each 300,000 units of penicillin G benzathine, mix well, being sure that all penicillin is in solution, and allow to stand for 15 minutes. Add 1 milliliter of 1.2*N* HC1 for each 2 milliliters of 0.5*N* NaOH, mix, and dilute with distilled water to obtain a concentration of 60 units of penicillin G procaine per milliliter. Transfer a 3.0-milliliter aliquot of this solution to a 50-milliliter volumetric flask and add 2 milliliters of water to give a volume of 5 milliliters.

(*c*) *Procedure.* Transfer respectively, 1.0, 2.0, 3.0, 4.0, and 5.0 milliliters of the standard procaine solution to each of five 50-milliliter volumetric flasks and transfer 5.0 milliliters of distilled water to a sixth 50-milliliter volumetric flask. Add 4.0, 3.0, 2.0, and 1.0 milliliters of water to the first four flasks, respectively, to give each a volume of 5 milliliters. To each flask of the standard and sample solutions, add 0.5 milliliter of 4*N* HC1, 1.0 milliliter of sodium nitrite solution, 1.0 milliliter of ammonium sulfamate solution, and 1.0 milliliter of *N*-(1-naphthyl)-ethylenediamine solution. Mix and wait two minutes after each addition. Dilute each flask to volume with distilled water. Using a suitable photoelectric colorimeter, determine the absorbancy of each solution at 550 nanometers. The instrument is balanced so that the zero concentration reads 0 absorbancy. Plot the standard curve on coordinate graph paper. Obtain the procaine penicillin content of the solution for assay directly from the point on the standard curve corresponding to its absorbancy.

(iii) *Penicillin G benzathine content.* The sum of the penicillin G procaine content determined as directed in paragraph (b)(1)(ii) of this section subtracted from the total potency determined as directed in paragraph (b)(1)(i) of this section represents the penicillin G benzathine content.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, medium F in lieu of medium E, and during the period of incubation, shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in §436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted aqueous suspension.

[42 FR 59868, Nov. 22, 1977, as amended at 43 FR 9799, Mar. 10, 1978; 50 FR 19918, 19919, May 13, 1985]

### § 440.255d Sterile penicillin G benzathine for suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G benzathine for suspension is a dry mixture of penicillin G benzathine and one or more suitable suspending or dispersing agents, and with or without one or more suitable preservatives and buffer substances. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not less than 5.0 percent and not more than 8.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the batch is packaged for repacking:

(*i*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*ii*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*2*) If the batch is packaged for dispensing:

(*i*) For all tests except sterility: A minimum of 10 immediate containers.

(*ii*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single–dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dissolve the portion thus obtained with sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately, further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Using the sample thus obtained, proceed as directed in § 436.205(b)(2) of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, and medium F in lieu of medium E. During the period of incubation shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in § 436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension obtained when the product is reconstituted as directed in the labeling.

[42 FR 59869, Nov. 22, 1977, as amended at 50 FR 19918, 19919, May 13, 1985]

### § 440.274 Penicillin G procaine injectable dosage forms.

### § 440.274a Sterile penicillin G procaine with aluminum stearate suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G procaine with aluminum stearate suspension is penicillin G procaine in a refined vegetable oil with one or more suitable and harmless dispersing agents and hardening agents. Each milliliter contains penicillin G procaine equivalent to 300,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. Its moisture content is not more than 1.4 percent. The penicillin G procaine used conforms to the standards prescribed by § 440.74a(a)(1). If the hardening agent is a refined hydrogenated and deodorized peanut oil, it is free from rancidity; it has an iodine value of not more than 10; its free fatty acid content as oleic acid is not more than one-tenth of 1 percent and its melting point is 64° C±2° C.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G procaine used in making the batch for potency, pyrogens, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, and moisture.

(ii) Samples required:

(*a*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 5 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place an accurately measured representative portion of the sample or the entire contents of a single-dose container into a 50-milliliter volumetric flask. Add 4 milliliters of chloroform and mix thoroughly. Dilute to volume with absolute ethyl alcohol. Mix well. Immediately further dilute with sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1 unit of penicillin G per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium B in lieu of medium A.

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

[42 FR 59870, Nov. 22, 1977, as amended at 50 FR 19919, May 13, 1985]

### § 440.274b Sterile penicillin G procaine suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G procaine suspension is an aqueous mixture of penicillin G procaine and one or more suitable suspending or dispersing agents, buffer substances, and preservatives. It may contain procaine hydrochloride in a concentration not exceeding 2.0 percent and one or more suitable stabilizing agents. Each container or each milliliter contains penicillin G procaine equivalent to not less than 300,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5. The penicillin G procaine used conforms to

the standards prescribed by §440.74a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G procaine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, and pH.

(ii) Samples required:

(*a*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dissolve the sample thus obtained in 50 to 100 milliliters of absolute methyl alcohol and add sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Immediately further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dissolve and dilute the sample thus obtained with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the prescribed concentration.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except add sufficient penicillinase to diluting fluid A and swirl the flask to completely solubilize the procaine penicillin before filtration. If the product contains lecithin, use diluting fluid D in lieu of diluting fluid A. If the product contains sodium carboxymethylcellulose, add sufficient sterile carboxymethylcellulase to diluting fluid A or D to completely solubilize the sodium carboxymethylcellulose before filtration. If the preparation contains homogenizers or suspending agents that prevent solubilization, proceed as directed in paragraph (e)(2) of that section, except use medium B in lieu of medium A.

(3) *Pyrogens.* Proceed as directed in §436.32(h) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *pH.* Proceed as directed in §436.202 of this chapter, using the undiluted drug.

[42 FR 59870, Nov. 22, 1977, as amended at 43 FR 9799, Mar. 10, 1978; 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### §440.274c Sterile penicillin G procaine for suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G procaine for suspension is a dry mixture of penicillin G procaine and one or more suitable suspending or dispersing agents, buffer substances, and preservatives. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not less than 2.8 and not more than 4.2

percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin G procaine used conforms to the standards prescribed by § 440.74a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G procaine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the batch is packaged for repacking:

(*i*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*ii*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*2*) If the batch is packaged for dispensing:

(*i*) For all tests except sterility: A minimum of 10 immediate containers.

(*ii*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: If it is packaged for repacking, dissolve an accurately weighed sample, equivalent to one dose, in 50 to 100 milliliters of absolute methyl alcohol and add sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. If it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dissolve the sample thus obtained in 50 to 100 milliliters of absolute methyl alcohol and add sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Immediately further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: If it is packaged for repacking, dissolve and dilute an accurately weighed sample, equivalent to one dose, with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the prescribed concentration. If it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dissolve and dilute the sample thus obtained with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the prescribed concentration.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except add sufficient penicillinase to diluting fluid A and swirl the flask to completely solubilize the procaine penicillin before filtration. If the product contains lecithin, use diluting fluid D in lieu of diluting fluid A. If the product contains sodium carboxymethylcellulose, add sufficient sterile carboxymethylcellulase to diluting fluid A or D to completely solubilize the sodium carboxymethylcellulose before filtration. If the preparation contains homogenizers or suspending agents that

prevent solubilization, proceed as directed in paragraph (e)(2) of that section, except use medium B in lieu of medium A.

(3) *Pyrogens.* Proceed as directed in §436.32(h) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in §436.201 of this chapter.

(6) *pH.* Proceed as directed in §436.202 of this chapter, using the suspension obtained when reconstituted as directed in the labeling.

[42 FR 59871, Nov. 22, 1977, as amended at 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### §440.280 Penicillin G potassium injectable dosage forms.

### §440.280a Sterile penicillin G potassium.

The requirements for certification and the tests and methods of assay for sterile penicillin G potassium packaged for dispensing are described in §440.80a.

[39 FR 18976, May 30, 1974, as amended at 42 FR 59871, Nov. 22, 1977]

### §440.280b Penicillin G potassium for injection.

(a) *Requirements for certification*— (1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium for injection is a dry mixture of penicillin G potassium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. Its pH is not less than 6.0 and not more than 8.5. If penicillin G potassium buffered is used, it conforms to the standards prescribed by §440.1080(a)(1). If penicillin G potassium is used, it conforms to the standards prescribed by §440.80a(a)(1) and the sodium citrate and citric acid conforms to the standards prescribed by the U.S.P.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, loss on drying, and pH.

(ii) Samples required:

(*a*) The penicillin G potassium, buffered, used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove or expel an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter, diluting an aliquot of the

stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter or, if the diluent is included in a disposable syringe combination, use the solution obtained when the drug is reconstituted as directed in the labeling.

[42 FR 59871, Nov. 22, 1977, as amended at 43 FR 9799, Mar. 10, 1978; 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### § 440.280c Penicillin G potassium injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium injection is a frozen, aqueous, iso-osmotic solution of penicillin G potassium which may contain one or more suitable and harmless buffer substances and a tonicity adjusting agent. Each milliliter contains penicillin G potassium equivalent to 20,000, 40,000, or 60,000 units of penicillin G. Its penicillin G content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.5 and not more than 8.0. The penicillin G potassium used conforms to the standards prescribed by § 440.80(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter. In addition, this drug shall be labeled ''penicillin G potassium injection''.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The penicillin G potassium used in making the batch for potency, loss on drying, pH, penicillin G content, and crystallinity.

(B) The batch for penicillin G content, sterility, pyrogens, and pH.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Penicillin G content.* Proceed as directed in § 440.280b(b)(1) of this chapter, except use the thawed solution.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 20,000 units of penicillin G per kilogram.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

[55 FR 38675, Sept. 20, 1990]

### § 440.281 Pencillin G sodium injectable dosage forms.

### § 440.281a Sterile penicillin G sodium.

The requirements for certification and the tests and methods of assay for sterile penicillin G sodium packaged for dispensing are described in § 440.81a.

[42 FR 59872, Nov. 22, 1977]

### § 440.281b Penicillin G sodium for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G sodium for injection is a dry mixture of penicillin G sodium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in

place of a corresponding amount of sodium citrate. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. Its pH is not less than 6.0 and not more than 7.5. The penicillin G sodium, buffered, used conforms to the standards prescribed by §440.1081a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G sodium, buffered, used in making the batch for potency, loss on drying, pH, penicillin G content, crystallinity, and heat stability.

(*b*) The batch for potency, sterility, pyrogens, loss on drying, and pH.

(ii) Samples required:

(*a*) The penicillin G sodium, buffered, used in making the batch: 10 packages, each containing approximately 60 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in §436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in §436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in §436.200(b) of this chapter.

(6) *pH.* Proceed as directed §436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

[42 FR 59872, Nov. 22, 1977; 43 FR 2393, Jan. 17, 1978, as amended at 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### §440.283 Sterile piperacillin sodium.

The requirements for certification and the tests and methods of assay for sterile piperacillin sodium packaged for dispensing are described in §440.83a

[47 FR 15770, Apr. 13, 1982]

### §440.290 Ticarcillin disodium injectable dosage forms.

### §440.290a Sterile ticarcillin disodium.

The requirements for certification and the tests and methods of assay for sterile ticarcillin disodium packaged for dispensing are described in §440.90a.

[43 FR 9800, Mar. 10, 1978. Redesignated at 50 FR 33518, Aug. 20, 1985]

### §440.290b Sterile ticarcillin disodium and clavulanate potassium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ticarcillin disodium and clavulanate potassium is a dry mixture of ticarcillin disodium and clavulanate potassium, in which the ratio of ticarcillin to clavulanic acid is 15:1 or 30:1. Its ticarcillin potency is not less

than 755 micrograms of ticarcillin per milligram on an anhydrous basis if the ratio is 30:1 and 733 micrograms of ticarcillin per milligram on an anhydrous basis if the ratio is 15:1. Its ticarcillin disodium content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of ticarcillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it contains not less than 85 percent and not more than 120 percent of the number of milligrams of clavulanic acid that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 4.2 percent. Its pH of an aqueous solution containing 100 milligrams per milliliter is not less than 5.5 and not more than 7.5. The ticarcillin disodium conforms to the standards prescribed by § 440.90a(a)(1) except that it contains not less than 840 micrograms of ticarcillin per milligram on an anhydrous basis. The clavulanate potassium conforms to the standards prescribed by § 455.15a(a)(1) of this chapter.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The ticarcillin disodium used in making the batch for potency, sterility, pyrogens, moisture, pH, and identity.

(*b*) The clavulanate potassium used in making the batch for potency, sterility, pyrogens, moisture, pH, identity, and clavam-2-carboxylate content.

(*c*) The batch for ticarcillin potency, ticarcillin content, clavulanic acid content, sterility, pyrogens, moisture, and pH.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) The ticarcillin disodium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*b*) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(*c*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: A minimum of 20 immediate containers collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Ticarcillin and clavulanic acid contents.* Determine micrograms of ticarcillin per milligram of sample and milligrams of both ticarcillin and clavulanic acid per container. Proceed as directed in § 436.355 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength between 220 and 230 nanometers, and a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded silicas. Reagents, working standard and sample solutions, system suitability requirements, and calculations for ticarcillin or clavulanic acid content are as follows:

(i) *Reagents*—(*a*) *0.1M Monobasic sodium phosphate buffer solution, pH 4.3.* Transfer 13.8 grams of monobasic sodium phosphate monohydrate to a 1-liter volumetric flask and dissolve in 900 milliliters of distilled water. Adjust the pH to 4.3±0.1 with 18*N* phosphoric acid or 10*N* sodium hydroxide. Dilute to volume with distilled water. Mix well.

(*b*) *Mobile phase.* Mix acetonitrile: 0.1*M* monobasic sodium phosphate buffer solution, pH 4.3 (5:95 v/v) and mix for no less than two minutes. Degas by passing through a 0.5-micrometer filter with vacuum. The mobile phase may be sparged with the helium through a 2-micrometer metal filter for the duration of the analysis. Adjust the ratio of acetonitrile to aqueous buffer as necessary to obtain satisfactory separation of the peaks.

(*c*) *Diluent.* 0.05*M* monobasic sodium phosphate buffer solution, pH 6.4 Transfer 6.9 grams of monobasic sodium phosphate to a 1-liter volumetric flask and dissolve in 900 milliliters of water. Adjust the pH to 6.4 with sodium hydroxide (10*N*). Dilute to volume with distilled water. Mix well. Use this diluent to prepare the working standard

and sample solutions described in paragraph (b)(1)(ii) of this section.

(ii) *Working standard and sample solutions)*—(*a*) *Preparation of working standard solution.* Accurately weigh a quantity of the ticarcillin working standard containing the equivalent of approximately 90 milligrams of ticarcillin activity and transfer into a 100-milliliter volumetric flask. Prepare a solution of the clavulanic acid working standard containing the equivalent of 30 milligrams or 60 milligrams of clavulanic acid activity in a 100-milliliter volumetric flask. Dissolve and dilute to volume with diluent. Transfer 10 milliliters of this solution into the flask containing the ticarcillin standard. Dilute the combined standard solution to volume with diluent. Mix. Use within 8 hours after preparation.

(*b*) *Preparation of sample solutions*—(*1*) *Ticarcillin potency (micrograms of ticarcillin per milligram).* Accurately weigh the total contents of a container and dissolve with sufficient diluent to obtain a stock solution containing approximately 30 milligrams of ticarcillin per milliliter. Further dilute this solution with diluent to obtain a final concentration of 0.9 milligrams of ticarcillin per milliliter (estimated).

(*2*) *Ticarcilin and clavulanic acid content (milligrams of ticarcillin and clavulanic acid per container).* Reconstitute the container with an appropriate volume of distilled water. Using a suitable hypodermic syringe, remove all of the withdrawable contents. Dilute with diluent to obtain a stock solution containing approximately 30 milligrams of ticarcillin per milliliter and 1 or 2 milligrams of clavulanic acid per milliliter. Further dilute this solution with the diluent to obtain a final concentration of 0.9 milligram of ticarcillin per milliliter. The final solution will contain either 0.03 or 0.06 milligram of clavulanic acid per milliliter (estimated) depending on the initial ticarcillin to clavulanic acid ratio.

(iii) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 2.0.

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,000 theoretical plates in a 25-centimeter column.

(*c*) *Resolution factor.* The resolution factor (*R*) between the clavulanic acid and ticarcillin peaks is satisfactory if it is not less than 5.0.

(*d*) *Coefficient of variation.* The coefficient of variation ($S_R$ in percent) is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in § 436.355(b) of this chapter.

(iv) *Calculations.* (*a*) Calculate the micrograms of ticarcillin per milligram as follows:

$$\text{Micrograms of ticarcillin per milligram} = \frac{A_u \times P_s}{A_s \times C_u}$$

where:

$A_u$=Area of the ticarcillin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ticarcillin peak in the chromatogram of the ticarcillin working standard;

$P_s$=Ticarcillin activity in the ticarcillin working standard solution in micrograms of anhydrous ticarcillin free acid per milliliter; and

$C_u$=Milligrams of sample per millilter of sample solution.

(*b*) Calculate the ticarcillin or clavulanic acid anhydrous free acid content of the container as follows:

$$\text{Milligrams of anhydrous ticarcillin or clavulanic acid free acid per container} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Area of the ticarcillin or clavulanic acid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ticarcillin or clavulanic acid peak in the chromatogram of the ticarcillin or clavulanic acid working standard;

$P_s$=Anhydrous ticarcillian or clavulanic free acid activity in the ticarcillin-clavulanic acid working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(*2*) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 100 milligrams of ticarcillin per milliliter.

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using a solution containing 100 milligrams per milliliter.

[50 FR 34418, Aug. 20, 1985; 50 FR 42156, Oct. 18, 1985; 50 FR 43384, Oct. 25, 1985; 50 FR 45403, Oct. 31, 1985, as amended at 55 FR 11582, Mar. 29, 1990]

### § 440.290c Ticarcillin disodium and clavulanate potassium injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ticarcillin disodium and clavulanate potassium injection is a frozen, aqueous, isoosmotic solution of ticarcillin disodium and clavulanate potassium with one or more suitable and harmless buffer substances. The ratio of ticarcillin to clavulanic acid is 30:1. Each milliliter contains ticarcillin disodium equivalent to 30 milligrams of ticarcillin and clavulanate potassium equivalent to 1 milligram of clavulanic acid. Its ticarcillin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of ticarcillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it contains not less than 85 percent and not more than 120 percent of the number of milligrams of clavulanic acid that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.5 and not more than 7.5. It passes the identity test. The ticarcillin monosodium monohydrate used conforms to the standards prescribed by § 440.91(a)(1). The clavulanate potassium used conforms to the standards prescribed by § 455.15(a)(1) of this chapter.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The ticarcillin monosodium monohydrate used in making the batch for potency, moisture, pH, identity, and crystallinity.

(B) The clavulanate potassium used in making the batch for potency, moisture, pH, identity, and clavam-2-carboxylate content.

(C) The batch for ticarcillin content, clavulanic acid content, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The ticarcillin monosodium monohydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(B) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(C) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Ticarcillin and clavulanic acid contents.* Proceed as directed in § 440.290b(b)(1), except use the thawed solution and prepare the sample solution and calculate the ticarcillin and clavulanic acid content as follows:

(i) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature. Dilute with diluent (described in § 440.290b(b)(1)(i)(*c*)) to obtain a solution containing approximately 0.9 milligram of ticarcillin activity per milliliter (estimated). This solution will contain approximately 0.03 milligram of clavulanic acid per milliliter. Introduce the sample into the chromatograph in a timely manner.

(ii) *Calculations.* Calculate the ticarcillin or clavulanic acid concentration as follows:

$$\text{Milligrams of ticarcillin or clavulanic acid activity per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

$A_u$=Area of the ticarcillin or clavulanic acid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$=Area of the ticarcillin or clavulanic acid peak in the chromatogram of the ticarcillin or clavulanic acid working standard;

$P_s$=Ticarcillin or clavulanic acid activity in the ticarcillin-clavulanic acid working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in § 436.20(e)(1).

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 100 milligrams of ticarcillin per kilogram.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(5) *Identity.* The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ticarcillin and clavulanic acid working standard.

[55 FR 5840, Feb. 20, 1990]

## Subparts D–J—[Reserved]

## Subpart K—Bulk Drug Formulations for Repacking or for Manufacturing Use

### § 440.1080a Sterile penicillin G potassium buffered.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium, buffered, is a dry mixture of penicillin G potassium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. The sodium citrate and citric acid used in making the batch must conform to all U.S.P. specifications. It is so purified and dried that:

(i) Its potency is not less than 1,355 units and not more than 1,595 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH is not less than 6.0 and not more than 8.5.

(vii) Its penicillin G content is not less than 76.3 percent and not more than 89.8 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

*(c) Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the

stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[42 FR 59872, Nov. 22, 1977, as amended at 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

### § 440.1081a Sterile penicillin G sodium, buffered.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G sodium, buffered, is a dry mixture of penicillin G sodium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. The sodium citrate and citric acid used in making the batch must conform to all U.S.P. specifications. It is so purified and dried that:

(i) Its potency is not less than 1,420 units and not more than 1,667 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH is not less than 6.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 80 percent and not more than 93.8 percent.

(viii) It is crystalline.

(ix) It passes the test for heat stability if it does not show a loss of more than 10 percent of its original potency.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, penicillin G content, crystallinity, and heat stability.

(ii) Samples required:

*(a)* For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

*(b)* For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

*(a) Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

*(b) Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

*(c) Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Heat stability.* Proceed as directed in § 436.214 of this chapter.

[42 FR 59873, Nov. 22, 1977; 43 FR 2393, Jan. 17, 1978, as amended at 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

# PART 441—PENEM ANTIBIOTIC DRUGS

## Subpart A—Bulk Drugs



## Subpart B—[Reserved]

## Subpart C—Injectable Dosage Forms



AUTHORITY: Sec. 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357).

## Subpart A—Bulk Drugs

### § 441.20a Sterile imipenem monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Imipenem monohydrate is the monohydrate form of [5*R*-[5α, 6α, (*R**)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl) amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid. It is a white to tan colored powder. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms and not more than 1,050 micrograms of imipenem per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its loss on drying is not less than 5.0 percent and not more than 8.0 percent.

(v) Its specific rotation in an aqueous solution containing 5 milligrams of imipenem per milliliter at 25 °C is +85° to +95° on an anhydrous basis.

(vi) It gives a positive identity test.

(vii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, specific rotation, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(*b*) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.216 of this chapter, using a column heater which will maintain a 50 °C column temperature, and ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octyl or octadecyl hydrocarbon bonded silicas, a flow rate of 2.0 milliliters per minute, and a known injection volume of 10 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(*a*) *Phosphate buffer, 0.001M.* Dissolve 272 milligrams of monobasic potassium phosphate in 1,800 milliliters of deionized water. Adjust the pH to 6.8 with 0.5*N* sodium hydroxide or dilute phosphoric acid. Dilute to 2,000 milliliters with deionized water and filter prior to use.

(*b*) *Mobile phase.* Dissolve 2.0 grams of 1-hexanesulfonic acid, sodium salt in 800 milliliters of phosphate buffer, 0.001*M*. Adjust the pH to 6.8 with 0.5*N* sodium hydroxide or dilute phosphoric acid and dilute to 1,000 milliliters with phosphate buffer, 0.001*M*. Filter and degas the mobile phase just prior to its introduction into the chromatograph pumping system.